Volume 83 Number 5 May 1996

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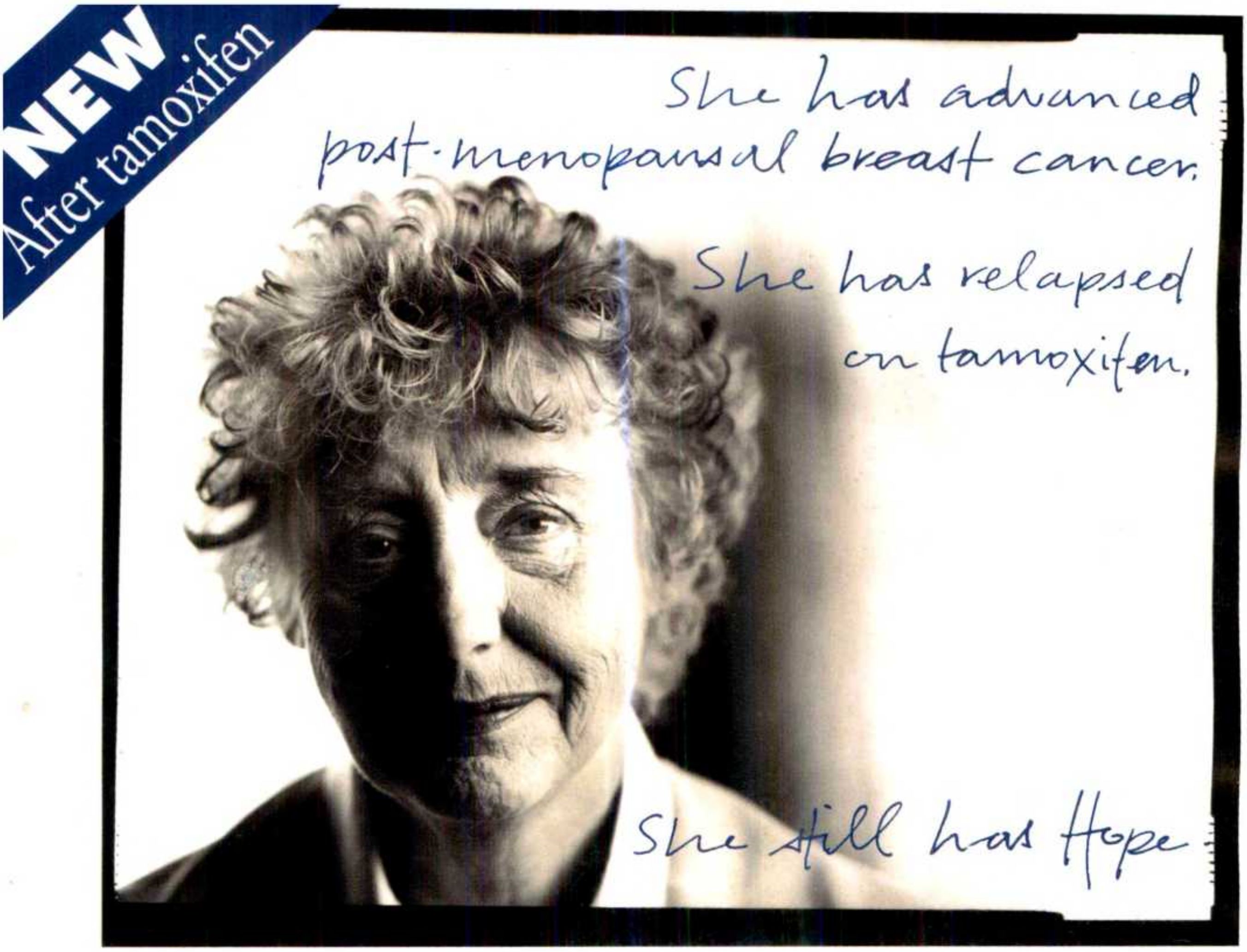
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P, 25, 348

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Reference: 1. Data on file.

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Typeset by Unicus Graphics Ltd
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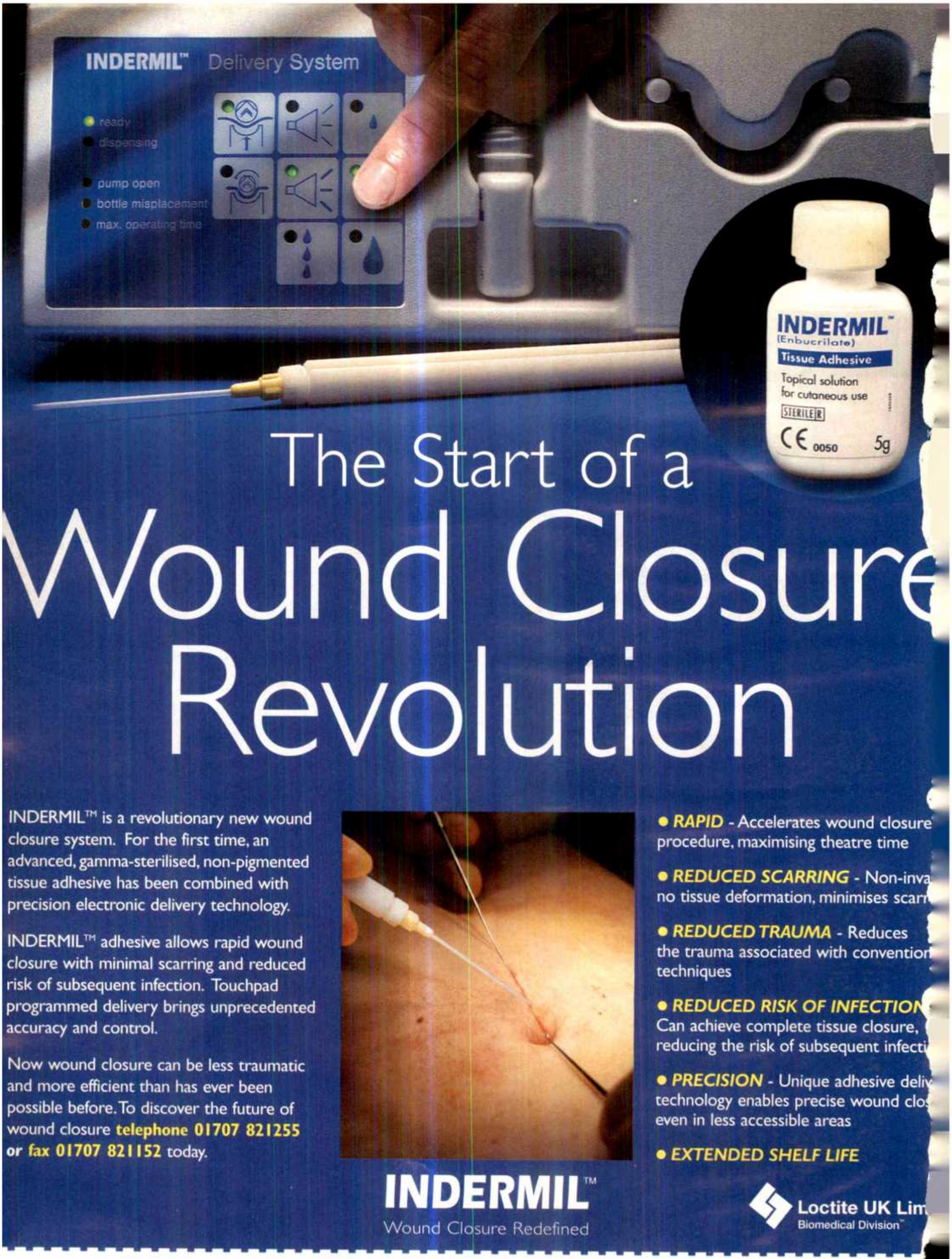

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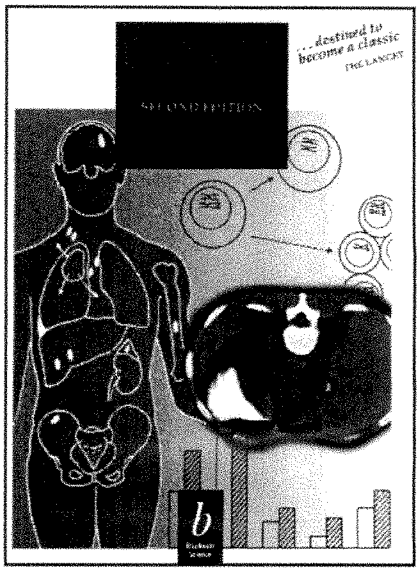

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First general meeting. A foundation meeting has already been held, and the founder members are listed below. The first annual meeting of EDS will take place in November 1996, during the United European Gastroenterology Week meeting in Paris. At that meeting an election will be held for officers and council members. The Society has established a transitional board to manage its affairs until the elected council can take over. Transitional board members are indicated on the list of founder members. Further information about EDS can be obtained from the founder members, and applications for membership should be made to European Digestive Surgery, c/o Karger AG, Allschwilerstrasse 10, PO Box, CH-4009 Basel, Switzerland.

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British Journal of Surgery 1996, **83**, 577–579

Leading articles

Management of soft tissue sarcoma

It is over 10 years since the management of soft tissue sarcoma was summarized for the *British Journal of Surgery*[1]. The present brief review emphasizes advances made in the past decade.

Aetiology and genetics

The rapid development of molecular biology, and the focus on genetic alterations that predispose to tumour development and progression, are especially obvious in the case of soft tissue sarcoma. Familial diseases such as neurofibromatosis, retinoblastoma and multiple polyposis have been associated with the development of this soft tissue tumour. The proposed genetic locus in Li–Fraumeni syndrome and retinoblastoma is p53. The relevance of such genetic abnormalities in diagnosis is obvious but they have yet to be exploited in terms of clinical management. In aetiology, the association between soft tissue sarcoma and antecedent radiation therapy[2], chemotherapy and lymphoedema has been described[3]. The risk from exposure to chemicals, particularly the dioxins, has been a matter of vigorous and emotional concern.

Prognosis

Approximately 50 per cent of soft tissue sarcomas presenting in adult patients occur in the extremities (*Fig. 1*). In the Memorial Sloan-Kettering Cancer Center analysis of approximately 2600 patients, the relevance of various factors that influence prognosis has been examined; this translates into alterations in the current established staging system. For example, a small, less than 5 cm lesion is historically placed in the American Joint Committee on Cancer staging system as a stage III lesion. However, analysis of small primary lesions treated appropriately suggests that outcome is sufficiently favourable for them to be considered as stage I lesions, with a less than 10 per cent chance of local recurrence and, for high-grade lesions, a less than 10 per cent chance of systemic disease[4]. For recurrent

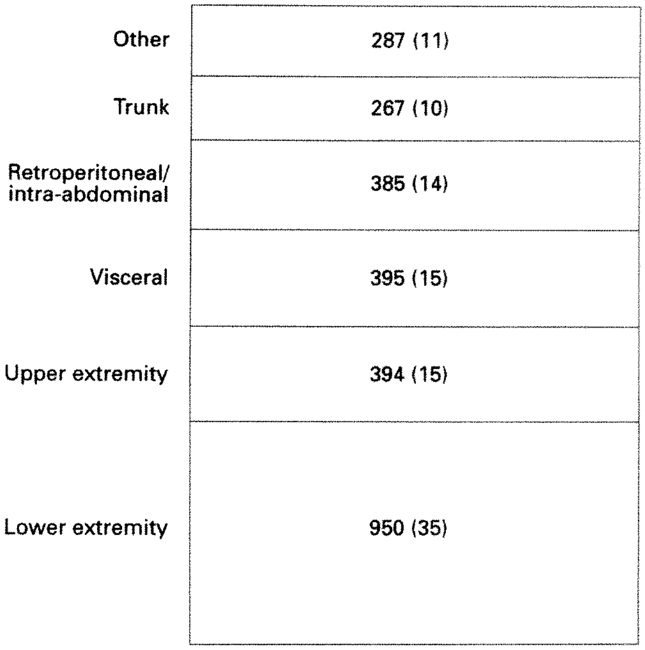

Fig. 1 Soft tissue sarcoma sites in 2678 patients presenting to Memorial Sloan-Kettering Cancer Center from 1 July 1982 to 1 July 1995. Values in parentheses are percentages

lesions or lesions with positive microscopic margins, these data are not valid; in such circumstances there is a greater risk of recurrence.

The importance of site is now firmly established and the outcome for extremity lesions is more favourable than that for retroperitoneal and visceral lesions. Whether this is inherent in the biology of the tumours, or purely a function of the size of the presenting lesions and/or the limitations to which aggressive therapy can be applied, is still under survey[3,5].

Outcome analysis

While overall survival remains the absolute standard, other analyses provide useful information. For example, when one is examining time to development of metastasis, the underlying histopathological grade of the lesion is more important than other aspects[6,7]. These data have been expressed historically as if such factors remained constant with time; it is now clear that such analyses are naive[6,7]. Metastasis-free survival is highly dependent on grade for approximately 2 years following diagnosis. After that period, other factors, particularly size, become as important as the grade of the original lesion in terms of the rate at which metastases develop. Factors increasing the probability of distant recurrence in extremity lesions include recurrent presentation, size greater than 5 cm, deep location, high grade and non-liposarcoma histopathology[7]. Time-honoured survival times of 3 and 5 years also appear imprecise. Approximately 9 per cent of patients disease free at 5 years eventually die from soft tissue sarcoma in the succeeding 5 years (J. J. Lewis *et al.*, unpublished results).

Treatment

It has been demonstrated clearly that the addition of adjunctive radiation therapy to surgical resection of extremity and superficial truncal soft tissue sarcoma decreases the likelihood of local recurrence[8]. Analyses from the author's centre suggest that the brachytherapy technique is effective, although of less impact on low- than on high-grade lesions[8]. External beam radiation therapy has been effective in limiting local recurrence in extremity sites in both high- and low-grade lesions. Strong arguments can be made that survival and outcome are improved if patients are treated at special centres[9].

Improvements in survival appear much less dramatic when factors associated with early detection and adequate treatment are excluded. Adjuvant trials of chemotherapy have been disappointing, with only isolated reports in selected series of improved survival. For retroperitoneal and visceral lesions, there has been little obvious improvement in outcome once improvement in operative mortality and complete resection rates are accounted for. Complete resection remains the dominant factor in the long-term outcome of these lesions[3,5]. Resection of metastatic disease is now being applied widely. In a large series of patients followed prospectively, the overall impact on all patients who developed pulmonary metastasis was small, with only 7 per cent alive at 3 years[10]. In visceral lesions, metastatic disease to the liver was helped only marginally by resection[11]. New immunological strategies are being developed and isolated lung perfusion, as therapy or adjuvant for a small group of selected patients, is being investigated.

Soft tissue sarcoma remains an ideal model for the investigation of strategies designed to improve long-term outcome. Advances in knowledge of aetiological predisposition continue to be made; multiple prognostic factors are being defined and the disease process is varied enough to provide a fertile field for treatment strategies.

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New members of the Editorial Board

Two surgeons from overseas have joined the Editorial Board of the Journal during 1995/96. We present a short synopsis of their biographical data and clinical interests.

PROFESSOR BERT EIKELBOOM
(The Netherlands)

Professor Bert Eikelboom joined the Editorial Board in 1995. He is Professor and Chief of Vascular and Transplantation Surgery at the University Hospital of Utrecht in the Netherlands. Born in 1947, he trained at Utrecht and Leiden and has worked in Surinam and New York as well as the Netherlands. He is a Past President of the Netherlands Society for Vascular Surgery and Associate Editor of the *European Journal of Vascular Surgery*. He is President Elect of the European Society for Vascular Surgery. Professor Eikelboom's major clinical interests are in vascular imaging, carotid endarterectomy and endovascular surgery.

PROFESSOR VLADIMIR FEDEROV
(Russia)

Professor Vladimir Dimitrievich Federov is Director of the AV Vishnevsky Institute of Surgery in Moscow, Russia. He was educated in Moscow and served as a Professor in the Moscow Medical Academy between 1960 and 1971. Thereafter he was Director of the Scientific Research Institute of Proctology until 1988, when he took up his present appointment. His clinical interests are in coloproctology, and his publications include a large personal experience of colonic polyposis.

British Journal of Surgery 1996, **83**, 580–581

Leading articles

Thrombolysis for acute deep vein thrombosis

Deep vein thrombosis (DVT) is a major health problem in the UK. Its incidence is difficult to ascertain as many cases go undetected, but it is probable that about 3 per cent of the population will have a DVT at some stage in their lives[1]. The most serious immediate risk associated with DVT is pulmonary embolism. Untreated, around 30 per cent of calf DVT and 50 per cent of proximal DVT will produce pulmonary emboli[2], of which 20–40 per cent will be fatal. Standard anticoagulation reduces the incidence of fatal pulmonary embolism to less than one in 1000.

In the long term it is estimated that over 60 per cent of patients develop symptoms of the post-thrombotic syndrome following an acute DVT, despite anticoagulation. This syndrome, associated with damage to the valves and subsequent venous hypertension, encompasses a range of symptoms and signs, from pain and swelling to skin pigmentation and venous ulceration. Venous ulcers probably develop in about 10 per cent of cases, although values as high as 48 per cent 2 years after an iliofemoral DVT have been quoted[3]. Such ulcers are a source of considerable morbidity in the community, with an estimated incidence of 1 per cent and a cost to the National Health Service of at least £100 million per annum (£1200 for each unhealed ulcer)[4].

Thrombolysis is an attractive treatment alternative to anticoagulation as it has the potential to lyse thrombus rapidly and may preserve valve function, thereby preventing the post-thrombotic syndrome in the long term. Much of the current thinking on the role of thrombolysis for thromboembolism is based on work carried out with streptokinase in the 1960s and 1970s. Streptokinase was typically given systemically over 3–5 days in roughly double the dose currently recommended. A pooled analysis by Goldhaber *et al.*[5] of six randomized trials of streptokinase *versus* heparin showed that thrombolysis was achieved 3·7 times more often in the groups treated with streptokinase, but bleeding complications occurred 2·9 times more often than with heparin[5]. Other reviewers agree that lysis is achieved to a much greater extent with streptokinase but maintain that the incidence of important bleeding complications is similar to that observed with full-dose heparin therapy (about 5 per cent)[6]. Whether thrombolysis confers any long-term benefit is more contentious. Kakkar and Lawrence[7] failed to demonstrate any significant benefit in 25 patients treated with streptokinase after a follow-up of 2 years. Others, particularly in the USA, have concluded[6] that 'the weight of evidence indicates that the post-phlebitic syndrome is often avoided by rapid, early and complete vascular reperfusion, especially in symptomatic patients with recently formed thrombi involving the popliteal or iliofemoral veins'.

Since these early trials there have been a number of developments in the field of thrombolysis, in particular the advent of new drugs such as urokinase and recombinant tissue-type plasminogen activator (rtPA), lower dosing regimens for systemic infusion and catheter-directed techniques of administration. These have improved success rates and reduced the complications of intra-arterial thrombolysis for acute limb ischaemia. Both rtPA and urokinase have also been used successfully in the treatment of acute DVT. In the largest trial to date with long-term follow-up, lysis was achieved in 45 per cent of patients receiving rtPA compared with 5 per cent of those receiving heparin; the incidence of post-thrombotic syndrome was 25 per cent in those with more than 50 per cent lysis, compared with 56 per cent in those with less than 50 per cent[8].

Perhaps most encouraging of all have been recent reports of catheter-directed techniques which deliver the thrombolytic agent to the site of the thrombus. Semba and Dake[9] treated 25 limbs with ileofemoral DVT in 21 patients. Approaching the thrombus usually from the internal jugular vein, they achieved complete lysis in 18 limbs (72 per cent) and partial lysis in a further five (20 per cent), with no major complications. Follow-up was limited, with only 12 patients reviewed at 3 months, but 11 of these had maintained patency. Interestingly, the group uncovered underlying venous anatomical abnormalities in more than half the patients, allowing secondary treatment with either angioplasty or stent placement. It may well be that this potential cause of rethrombosis can be more readily identified and treated with the more intensive imaging used with catheter-directed techniques. The risk of pulmonary embolism during catheter-directed thrombolysis has not been established; Semba and Dake[9] did not report this as a problem and, indeed, it has not been a feature of most of the numerous reports of systemic thrombolysis. Nevertheless, one trial investigating the effectiveness of a new temporary vena caval filter in patients undergoing thrombolysis demonstrated clot within the filter in 25 per cent of patients[10]. Until the risk of pulmonary embolism is properly determined it seems prudent to use a temporary filter in all cases.

How many patients will be eligible for thrombolysis? Markel and colleagues[11], in a retrospective review of 209 patients with DVT, concluded that only 7 per cent did not have a contraindication to thrombolysis. While many would argue with some of their definitions of a contraindication, a large number of patients are clearly unsuitable for thrombolysis. It is probable that patients with either a previous history of DVT or a history of thrombosis of greater than 2 weeks already have significant valvular damage and so have little to gain from a procedure aimed at preventing valvular compromise. These patients should be excluded, as should those with active internal bleeding or bleeding diathesis, recent cerebrovascular accident or intracranial metastases. Patients with relative contraindications to thrombolysis, such as recent major surgery or invasive procedures, or pregnancy, need to be considered in the light of the risks of bleeding associated with the alternative treatment (anticoagulation). The question that remains is whether a system of catheter-directed thrombolysis can be developed that is sufficiently user-friendly to allow widespread application in centres remote from highly developed endovascular departments. Only with such a system will the potential impact of thrombolytic therapy on the widespread morbidity associated with acute DVT be fully realized.

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British Journal of Surgery 1996, 83, 582–587

Review

Ultrasonographic carotid plaque morphology in predicting stroke risk

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A number of new studies have provided evidence which suggests that carotid plaque surface characteristics and internal structure, as seen on ultrasonography, contribute to the development of cerebrovascular endpoints. This review is a critical presentation of the evidence that has emerged so far supporting the hypothesis that the ultrasonographic morphology of the carotid plaque may be an independent variable in predicting the risk of stroke. It is concluded that ultrasonographic plaque morphology should be used together with other local risk factors in prospective natural history studies which aim to identify a subgroup of patients at high risk of stroke.

Both the European Carotid Surgery Trial[1] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[2] investigators reported a conclusive benefit for carotid endarterectomy over medical management in patients with symptomatic internal carotid artery stenosis of 70–90 per cent. In these studies the degree of angiographic stenosis of the internal carotid artery was the only criterion for selection of symptomatic patients at high risk of stroke. A subsequent report from the NASCET investigators[3] has indicated that the presence of ulceration at each level of stenosis, as seen on the angiogram, resulted in higher stroke rates than those associated with lesions without ulceration. Other studies, using ultrasonography to characterize carotid bifurcation plaque in asymptomatic patients, have suggested that echolucent plaque is associated with an increased risk of stroke[4–6].

It appears that certain features of atherosclerotic plaque are associated with an increased risk of stroke; most of these features can now be determined non-invasively by ultrasonography. This article reviews the literature on the ultrasonographic characterization of carotid plaque, with particular emphasis on its clinical importance. The morphological variables are grouped in two categories: (1) plaque surface configuration (smooth or ulcerated); and (2) plaque internal structure.

Plaque surface configuration

Definitions

No uniform agreement exists on the definition of ulceration. However, a definition is important to avoid a falsely high incidence being reported as a result of the inclusion of lumen surface irregularity. Another factor that might increase the apparent incidence of ulceration is the inclusion of smaller ulcers, noted when operative specimens are examined under magnification[7]. The lack of an agreed definition is one of the reasons for the great diversity in the reported incidence of carotid plaque ulceration. While some studies do not give a definition of plaque ulceration[8], others use differing definitions. According to Yao and colleagues[9], an ulcerated plaque is a complex (mixed) plaque which has variable echogenicity within it. Others have suggested that the ultrasonographic characteristics of the plaque surface should be classified into smooth or irregular. A plaque is regular when the blood–lesion interface is smooth and unbroken, and irregular where a break in the echoreflective surface of the lesion is observed or the surface is uneven[10]. Some authors have defined carotid plaque ulceration according to the gross pathology of the endarterectomy specimen, such as crater width and depth of 1 mm or more[7], or a definite surface irregularity with a punched-out characteristic[11]. Moore and co-workers[12,13] have defined ulceration based on measured size and area calculations using conventional cut-film angiography. Ulcer size may be obtained by multiplying the length and width of the ulcer in millimetres. Ulcers measuring less than 10 mm^2 are defined as 'A' ulcers, ulcers of 10–40 mm^2 as 'B' ulcers, and those exceeding 40 mm^2 as 'C' ulcers. Definitions based on endarterectomy specimen histology, used as the 'gold standard', also vary from area of loss of surface endothelium[14] to deep undermining depressions in the plaque[15].

Standardization of definition for each methodology is a logical prerequisite in any comparative study. Criteria used to date in published studies are often not comparable and results must be interpreted with this in mind.

Detection of ulcerated plaque

Preoperative diagnosis of ulcerated carotid atheroma has attracted the interest of many investigators in an attempt to identify a group at high risk of stroke. O'Donnell and selective arteriography with pathological specimens obtained from 89 carotid endarterectomies. While arteriography detected only 16 of 27 ulcerations (sensitivity 59 per cent), B-mode ultrasonography detected 24 of 27 (sensitivity 89 per cent). Both imaging techniques had comparable specificities (arteriography 73 per cent, ultrasonography 87 per cent). Others have not confirmed the high sensitivity of ultrasonography in detecting ulcerated carotid atheroma. O'Leary *et al.*[16] used intact endarterectomy specimens as their gold standard. B-mode ultrasonography had a sensitivity of only 39 per cent and

Paper accepted 7 November 1995

specificity of 72 per cent for the prediction of ulceration[16]. Better results were reported by Yao *et al.*[9]. When the surgical specimen was used as the reference standard, B-mode scanning detected ulcerating plaque in 46 (54 per cent) of 85 patients. The sensitivity for arteriography was 42 per cent. The discrepancy in the above studies may be the result of different definitions used for ulceration. According to O'Donnell *et al.*[11] ulceration is a definite surface irregularity with punched-out characteristics; O'Leary *et al.*[16] suggested that an ulcer should have a diameter and depth of more than 1 mm on macroscopic examination. However, such small ulcers may not have been visible with the old generation of duplex scanners. Furthermore, the identification of such a small size of ulcer may have only limited clinical significance. Moore *et al.*[12] classified 72 angiographically ulcerated carotid plaques in 72 patients into types A, B and C ulcers. The annual stroke rate over 7 years was 0·4 per cent per year for minimal type A ulcers and 12·5 per cent per year for types B and C. The same group, in a further analysis of the natural history of 153 non-stenotic asymptomatic ulcerative lesions of the carotid artery, reported an annual stroke rate of 4·5 per cent for type B and 7·5 per cent for type C ulcers[13].

The above studies investigating the ability of B-mode carotid imaging to detect ulceration have failed to address the associated quantitative aspect of carotid plaque. A recent study[7] has shown that the degree of stenosis significantly affects diagnostic sensitivity. B-mode sensitivity for the presence of ulceration was 77 per cent (ten of 13) in plaques of 50 per cent or less stenosis, and only 41 per cent (26 of 63) in plaques of greater than 50 per cent stenosis ($P = 0{\cdot}03$). The values for arteriography were 77 per cent (ten of 13) and 48 per cent (30 of 63) respectively.

In a subsequent study[17] the repeatability of ultrasonographic diagnosis of carotid ulceration by the same observer was found to be moderate ($k = 0{\cdot}64$). When the interpretations of two observers were compared, the value of k fell to 0·11. Similar degrees of reproducibility were noted using angiographic techniques, with intraobserver repeatability of $k = 0{\cdot}67$ and interobserver repeatability of $k = 0{\cdot}41$. In the NASCET study[3] the intraobserver variability in classifying plaques angiographically into ulcerated, uncertain ulceration and smooth had a k value of 0·73. The data from the above studies do not allow a definite conclusion to be made as to whether B-mode ultrasonography is or is not a better technique than angiography for the identification of ulcerated atheroma. Currently both techniques seem to have a sensitivity of approximately 50 per cent. In addition, it appears that the ultrasonographic criteria for the diagnosis of ulcerated carotid atheroma are subjective and not easily transferable from one centre or interpreter to another. This may have important implications in the design of multicentre trials on carotid disease which include ultrasonography.

Lusby[18] has stated that 'duplex scanning has the ability to detect the degree of stenosis based on Doppler spectral analysis and the morphological appearance of the plaque in terms of echolucent and echodense areas. Whether this modality could be asked to go beyond this by detecting surface ulceration may require more than it is capable of doing'. However, the introduction of a new generation of duplex scanners with edge-enhancing capabilities may considerably improve the accuracy of ultrasonography in the identification of carotid plaque ulceration.

Clinical significance

Julian and colleagues[19] in 1963 were the first to discuss the issue of carotid plaque ulceration. They reported 17 cases of macroscopic ulcerative carotid lesions in 231 symptomatic patients who had undergone carotid endarterectomy. Macroscopic thrombi were noted lying in the ulcer crater in all cases. The authors suggested that carotid plaque ulceration might be associated with an increased risk of cerebral embolism. Similar findings were reported by Moore and Hall[20] and others[21,22] who have stressed the importance of plaque ulceration in the development of symptoms. However, this pattern has not been consistent. Imperato *et al.*[23], in a series of 275 symptomatic and 101 asymptomatic plaques obtained from carotid endarterectomies, did not find any significant difference in the incidence of ulceration between the symptomatic (132 of 275) and asymptomatic (41 of 101) plaques. In this study only intraplaque haemorrhage was significantly more frequent in symptomatic than in asymptomatic plaques. A clinicopathological study[24] on a small number of patients failed to demonstrate a difference in the incidence of histologically confirmed ulceration in patients with transient ischaemic attacks (eight of 26) and in those with no symptoms (nine of 33).

A reason for these conflicting reports may be differing time intervals between the occurrence of symptoms and operation. This time interval was not recorded in any of the above studies. Lusby *et al.*[25] reported re-endothelization in several plaques when the interval between symptom onset and operation was longer than 3 weeks. It may be that some ulcers heal after a single transient ischaemic attack or amaurosis fugax. The authors believe that this point should be addressed in future studies.

In an early study[8], carotid endarterectomy specimens were examined with the naked eye for macroscopic ulceration and the findings correlated with the prevalence of cerebral infarction on computed tomography (CT) in 65 patients who underwent 68 carotid endarterectomies. Fifty-five specimens were removed from the symptomatic and 13 from the asymptomatic side. A macroscopic ulcer was found in 42 specimens. Twenty-six patients (62 per cent) with ulceration had one or more ipsilateral infarcts. In contrast, only two (8 per cent) of 26 patients without ulceration had infarcts. These data demonstrate a strong association between internal carotid plaque ulceration and cerebral infarction detected by CT. Further evidence of the clinical importance of ulcerative carotid lesions is provided by the NASCET[26]. Review of 593 angiograms with severe stenosis led to recognition of ulceration with reasonable certainty in 34 per cent of those assigned to the medical group and in 36 per cent of those assigned to surgery. At 2 years, a non-fatal stroke or vascular death had occurred in 30 per cent of the group with ulcer assigned to medical care alone, but in only 17 per cent of those without an ulcer ($P = 0{\cdot}005$, log rank test).

It appears from the above studies that the presence of carotid plaque ulceration may be of clinical relevance. Its potential for identifying a group at a high risk of stroke among patients with asymptomatic internal carotid stenosis should be explored.

Consistency of the plaque

Background

High-resolution ultrasonography has the major advantage over angiography that it allows assessment not only of the lumen, but also of the size and consistency of an atherosclerotic plaque. One of the early classifications of carotid plaques was introduced by Johnson *et al.*[4] in 1985 in a study of the natural history of patients with asymptomatic carotid stenosis followed for 3 years. Three types of plaques were described: calcified, dense (high-level echoes) and soft (low-level echoes). The results of this study are summarized below under 'Clinical significance'.

Another classification that allows a closer study of the character and behaviour of plaques was introduced by Reilly *et al.*[27] in 1983 and subsequently used by others[28]. Two distinct types of plaque were recognized. The first was termed homogeneous and was defined as a plaque with uniformly high- or medium-level echoes. Homogeneous plaques were, histologically, fibrous lesions. The second type was termed heterogeneous and was defined as a plaque with high-, medium- and low-level echoes. Histologically, heterogeneous plaque contained variable amounts of intraplaque haemorrhage, lipids, cholesterol crystals and a loose stroma[27].

A refinement of the above classification was introduced by Gray-Weale *et al.*[29] in 1988. Four plaque types were defined based on the degree of echolucency seen on B-mode scan:

Type 1: Dominantly echolucent with a thin echogenic cap.
Type 2: Substantially echolucent with small areas of echogenicity.
Type 3: Dominantly echogenic with small areas of echolucency (less than 25 per cent).
Type 4: Uniformly echogenic (equivalent to homogeneous).

The authors' group[30] has added a type 5 for plaques that cannot be classified owing to acoustic shadowing artefact; good interobserver agreement was reported ($k=0\cdot79$). Furthermore, it has been realized that when carotid stenosis is greater than 70 per cent, 69 per cent of type 1 plaques do not have a thin echogenic cap and may be missed unless velocity measurements are made or colour flow imaging is used[31].

Studies correlating histological characteristics with B-mode ultrasonographic imaging of carotid plaques have shown that echogenic plaques are fibrous. The echogenicity increases with an increasing amount of collagen. Echolucent plaques contain lipid and/or haemorrhage, with relatively little fibrous tissue. The presence of calcification results in high echoes in corresponding areas with extensive acoustic shadowing[11,32,33]. Pathological studies have demonstrated that increased lipid concentration makes carotid plaques unstable and prone to embolism[34,35]. Similar findings have been reported in a cadaveric study, in which ulceration and thrombosis were characteristic of aortic plaques, which contained a high proportion of lipid, in contrast to fibrous plaques[36].

Because intraplaque haemorrhage produces echolucent areas in plaques, its clinicopathological significance merits close examination. The association between intraplaque haemorrhage in endarterectomy specimens and ipsilateral symptoms has been reported by several groups (*Table 1*). There is general agreement that intraplaque haemorrhage is common in all plaques, but its incidence is increased in those associated with ipsilateral symptoms. *Table 1* suggests that differences in the incidence of haemorrhage between symptomatic and asymptomatic plaques depends on the definition of intraplaque haemorrhage. Recent and large haemorrhages are more common in symptomatic plaques. In one study[37], although there was no significant difference in the incidence of intraplaque haemorrhage in symptomatic and asymptomatic plaques, there was a higher incidence (86 per cent) in stenotic than in non-stenotic (41 per cent) plaques ($P<0\cdot03$). Attempts to distinguish between intraplaque haemorrhage and lipid by means of ultrasonography have so far been unsuccessful but, clinically, this may not be critical as both features render the plaque potentially unstable[18].

Steffen *et al.*[38] reported that in symptomatic arteries, for all degrees of stenosis, there is a preponderance (67 per cent) of echolucent type 1 and 2 lesions; in patients without symptoms there is a majority (86 per cent) of echogenic type 3 and 4 plaques. Geroulakos *et al.*[30] have confirmed these findings in patients with stenosis greater than 70 per cent. In addition, these authors have demonstrated on CT that patients with more than 70 per cent stenosis have an increased incidence of cerebral infarction ipsilateral to type 1 plaques (36 per cent). This may be compared with a low incidence (14 per cent) of infarction ipsilateral to all other types (2–4) combined ($P<0\cdot03$)[39]. It is tempting to speculate that the different incidence of cerebral infarction associated with the various ultrasonographic types of plaque may reflect a different incidence of carotid plaque ulceration and intraplaque haemorrhage. Indeed, Gray-Weale *et al.*[29], in a study of 220 patients who underwent 244 carotid endarterectomies, showed a significant relationship ($P<0\cdot001$) between echolucent plaques, as seen on preoperative B-mode ultrasonography, and the presence of either intraplaque haemorrhage or ulceration in the endarterectomy specimen. Of 179 lesions classified as type 1 or 2, 174 (97 per cent) contained intraplaque haemor-

Table 1 Incidence of intraplaque haemorrhage in endarterectomy specimens and its association with ipsilateral symptoms

Reference	Year	Symptomatic patients	Asymptomatic patients	Definition of haemorrhage
Lusby *et al.*[25]	1982	49 of 53 (92)	7 of 27 (26)	Acute (1 week) Recent (1–6 weeks)
Imperato *et al.*[23]	1983	94 of 275 (34)	21 of 101 (21)	Macroscopic (all types)
Fisher and Ojemann[24]	1986	25 of 44 (57)	6 of 33 (18)	Recent (all types)
Fryer *et al.*[14]	1987	66 of 71 (93)	12 of 12 (100)	All types
		40 of 71 (56)	3 of 20 (15)	Recent and large (>50 per cent of plaque thickness)
		18 of 71 (25)	6 of 20 (30)	Recent and small (<50 per cent of plaque thickness)
		51 of 71 (72)	10 of 20 (50)	Old haemorrhage
Bassiouny *et al.*[37]	1989	33 of 45 (73)	19 of 31 (61)	All types

Values in parentheses are percentages

rhage or were ulcerated. The echographic assessment of plaque structure in all the studies quoted above was based on a subjective qualitative evaluation of the plaque. Recently, two techniques have been introduced which permit a quantitative objective assessment of the ultrasonographic characterization of atherosclerotic plaque.

In vitro videodensitometric analysis of B-mode images of arteries has shown increased grey-level intensities in fibrous plaque compared with plaque with a high concentration of cholesterol and necrotic material[40]. Although this method has the potential for clinical application, it has not yet been used for carotid plaque characterization.

Radiofrequency-based ultrasonographic tissue characterization has been used *in vitro* to analyse images of carotid plaque. The authors used a display of the number of pixels at different grey-scale levels and found different distributions according to the predominant content of the plaque (lipid, fibrous or calcified components)[41]. This relatively simple, quantitatively displayed, information represents an improvement for future studies of carotid plaque characterization, as it provides an assessment of structure that is independent of the observer. A similar approach was used in an *in vitro* study of 148 plaques in 87 patients causing a greater than 50 per cent stenosis. All patients had brain CT and the presence or absence of infarction in the ipsilateral middle carotid artery territory was noted. For each plaque, a histogram was obtained with the number of pixels plotted against the gray scale (0–255; 0 = black, 255 = white). The median of the gray scale was used as a measure of echogenicity. Plaques with a gray scale median higher than 32 were associated with an incidence of cerebral infarction of 11 per cent (seven of 64). In contrast, plaques with a gray scale median lower than 32 were associated with an incidence of cerebral infarction of 55 per cent (46 of 84) ($P<0{\cdot}001$)[42]. In a subsequent study, the relationship between heterogeneity (or homogeneity) of plaque and the incidence of CT-recognized brain infarcts was investigated. Using similar computer analysis, the most echogenic area of each plaque was compared with the most echolucent area. The difference of the median values of the gray scale between the two areas was used as an index of heterogeneity. There was no relationship between heterogeneity and the incidence of cerebral infarct[43]. The overall amount of echolucent area appears to correlate with the incidence of infarction rather than whether the plaque is homogeneous or heterogeneous. So far, computer analysis promises to be useful. It should be used in addition to the degree of stenosis in prospective studies on the natural history of asymptomatic carotid stenosis and the risk of stroke.

Clinical significance

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Despite the extensive work undertaken by many groups on the significance of ultrasonographic plaque patterns and their correlation with histology, there are only three natural history studies that associate ultrasonographic plaque structure with clinical events.

As mentioned earlier, the first prospective study was reported by Johnson *et al.*[4] in 1985. Asymptomatic plaques were classified, according to ultrasonographic characteristics, into calcified, dense and soft. At the end of a 3-year follow-up, 40 of 42 patients with (initially) no symptoms and soft plaques causing more than 75 per cent stenosis had become symptomatic. By contrast, only five of 42 patients with calcified plaques causing more than 75 per cent stenosis developed ipsilateral symptoms (*Table 2*).

Table 2 Incidence of cerebrovascular events in patients with asymptomatic carotid artery stenosis according to ipsilateral plaque morphology

Type of plaque	Stenosis (%)	No. of patients	No. of TIAs	History of stroke
Calcified	>75	37	4	0
	<75	53	0	0
Dense	>75	42	22	4
	<75	76	5	0
Soft	>75	42	31	10
	<75	47	7	3

TIA, transient ischaemic attacks. From Johnson *et al.*[4] (modified)

Johnson's study was the first to indicate that the risk of developing symptoms and stroke was increased not only by the presence of high-grade stenosis, but also by the ultrasonographic character of the plaque. These findings were confirmed by Sterpetti *et al.*[5], who studied 135 asymptomatic and 79 symptomatic patients, with a total of 238 carotid plaques. During a mean follow-up of 34 months, the total number of events in patients with less than 70 per cent stenosis was 13 of 134 (10 per cent) of which eight were transient ischaemic attacks and five were strokes. In patients with greater than 70 per cent stenosis, the total number of events was 12 (27 per cent) of 44, of which six were transient ischaemic attacks and six were strokes. Nineteen events (27 per cent) occurred in 71 patients with heterogeneous plaques, while only six (4 per cent) occurred in 167 with homogeneous plaques. Multivariate analysis showed that the ultrasonographic pattern (heterogeneous plaques consisting of mixed high-, medium- and low-level echoes) and the severity of stenosis were independent variables. Recently, in a prospective series of 242 patients, Bock *et al.*[6] found that vessels with echolucent carotid plaques were associated with a 5·7 per cent annual rate of transient ischaemic attacks and stroke; this was significantly greater than the rate of 2·4 per cent found for vessels with echogenic plaques.

The above reports provide some evidence to suggest that the ultrasonographically visualized internal structure of the carotid plaque is a factor that may contribute to the development of cerebrovascular endpoints.

Conclusions

Indications for carotid endarterectomy should be better defined. A description of patients who are likely to derive maximal benefit is needed. To achieve this, stratification of patients into risk-of-stroke categories is required. There is now strong evidence to suggest that ultrasonographically derived carotid plaque surface characteristics and internal structure are factors that contribute to the development of cerebrovascular endpoints. No prospective study has yet assessed the combined effect of degree of stenosis, ultrasonographic plaque characterization and the status of the collateral cerebral reserve[44] on the incidence of ipsilateral stroke. Such a natural history study is urgently needed and should be performed in asymptomatic patients with severe carotid stenosis, since ethical considerations preclude future natural history studies in symptomatic patients with critical stenosis. Identification of a subgroup at high risk should lead to the refinement of the selection criteria for operation. This should increase the therapeutic benefit from carotid endarterectomy by reducing the number of unnecessary procedures.

Acknowledgements

The authors express appreciation to Professor J. Lumley for constructive criticism.

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British Journal of Surgery 1996, 83, 588–601

Review

Adhesion molecules as determinants of disease: from molecular biology to surgical research

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Cellular adhesion is mediated by distinct cell surface receptors (adhesion molecules) and plays a pivotal role in the biological processes of morphogenesis, cell migration and cell–cell communication. During the past decade many adhesion molecules have been identified and structurally analysed. This has allowed an understanding of their role in the pathophysiology of disease, including inflammation and sepsis, ischaemia and reperfusion, transplant rejection, atherosclerosis and thrombosis, angiogenesis and wound healing, as well as carcinogenesis and tumour metastasis. Understanding of the molecular mechanisms of cellular communication is not only vital for advances in surgical pathophysiology, it also has the potential to widen the spectrum of diagnosis and therapy of disease. Analysis of expression of individual surface molecules may help in the diagnosis of transplant rejection and allow a prognostic determination of tumour progression and metastasis formation. Moreover, manipulation of adhesion molecule function by monoclonal antibodies, antisense oligonucleotides or single gene products may open the door for novel therapeutic regimens to prevent transplant rejection and ischaemia-, sepsis- and shock-induced tissue injury.

The ability to study the cellular and molecular basis of cell–cell interaction has not only influenced the spectrum of basic research, but also challenges the surgeon to seek a more detailed understanding of the pathophysiology of disease, including sepsis and shock, ischaemia–reperfusion, transplant rejection, atherosclerosis and thrombosis, as well as carcinogenesis and tumour metastasis. During the past decade many cell-surface receptors (adhesion molecules) mediating cell–cell interaction have been identified and structurally analysed using molecular biology techniques. It is now time to incorporate this knowledge into surgical research and to determine the functional relevance of these molecules, both under normal conditions and in disease.

A fundamental requirement of multicellular organisms is a recognition system to guide the interaction between individual cells and so regulate processes such as morphogenesis, healing and host response. The expression, regulation and function of adhesion molecules play a crucial role in these complex events and dysfunction or dysregulation will, consequently, result in manifestation of disease. The specific function of the individual molecules and the interaction of one with the other result in highly differentiated biomolecular cascades and networks; these must be identified in order to elucidate physiology and to understand the process of pathology.

Adhesion molecules are classified in four groups according to their biochemical structure: integrins, immunoglobulin-like proteins (immunoglobulin gene superfamily), cadherins and selectins. This paper reviews the characteristics of the individual molecules of these groups, their role in surgical pathophysiology and potential therapeutic consequences.

Adhesion molecules

Adhesion molecules of the integrin superfamily

Integrins are transmembrane cell-surface proteins that bind to cytoskeletal proteins and communicate extracellular signals[1]. They consist of non-covalently linked, heterodimeric α and β chains that mediate cell adhesion. They are grouped in subfamilies according to the β subunit (*Table 1*) and, due to association with different α subunits, as many as 21 different integrin combinations are known[2]. Certain of the integrins function as extracellular matrix receptors, others mediate leucocyte–endothelial cell adhesion or bind primarily to matrix proteins of inflammation, wound healing and development[3]. The cells of most tissues express $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$ and $\alpha_6\beta_1$, while the $\alpha_5\beta_1$ fibronectin receptor is primarily expressed on endothelial cells of large vessels. Epithelial cells contain α_V in association with β_5 and β_6 subunits rather than the vitronectin receptor $\alpha_V\beta_3$[4,5]. Leucocytes express β_2 integrins as well as $\alpha_4\beta_1$, $\alpha_4\beta_7$, $\alpha_5\beta_1$ and $\alpha_6\beta_1$[6–10], while $\alpha_{IIb}\beta_3$ is expressed primarily on platelets[11].

β_1 integrins. The β_1 integrins, which share CD29 as their common β subunit[6], bind primarily to extracellular matrix proteins, including fibronectin, collagen, laminin, thrombospondin and vitronectin[9]. However, the $\alpha_4\beta_1$ integrin has also been shown to mediate adhesion of lymphocytes[12–14], monocytes[15,16], eosinophils[17,18], basophils[17,18] and natural killer (NK) cells[19] to activated endothelium by binding to vascular cell adhesion molecule (VCAM) 1[10,12]. Neutrophils alone do not express $\alpha_4\beta_1$ integrins[6] and so cannot use this pathway to interact with endothelial cells.

β_2 integrins. The expression of the β_2 integrins, which share CD18 as their common β subunit[20], is primarily restricted to leucocytes. However, their distribution differs among subtypes of these cells: $\alpha_L\beta_2$ is mainly expressed on

Paper accepted 3 November 1995

Table 1 Adhesion molecules of the integrin superfamily

Integrin	Other names	Ligand
$\alpha_1\beta_1$	CD49a–CD29	Laminin (collagen)
$\alpha_2\beta_1$	CD49b–CD29, gpIa–IIa	Collagen (laminin)
$\alpha_3\beta_1$	CD49c–CD29	Fibronectin, laminin, collagen
$\alpha_4\beta_1$	CD49d–CD29	VCAM-1, fibronectin
$\alpha_5\beta_1$	CD49e–CD29, fibronectin receptor	Fibronectin
$\alpha_6\beta_1$	CD49f–CD29, laminin receptor	Laminin
$\alpha_7\beta_1$		Laminin
$\alpha_8\beta_1$		
$\alpha_V\beta_1$	CD51–CD29	Fibronectin
$\alpha_L\beta_2$	CD11a–CD18, LFA-1	ICAM-1, ICAM-2, ICAM-3
$\alpha_M\beta_2$	CD11b–CD18, Mac-1	ICAM-1, ICAM-3, fibrinogen, C3bi
$\alpha_X\beta_2$	CD11c–CD18, p150, 95	Fibrinogen, C3bi
$\alpha_{\mathrm{IIb}}\beta_3$	CD41a, gpIIb–IIIa	Fibrinogen, fibronectin, vitronectin, von Willebrand factor
$\alpha_V\beta_3$	CD51–CD61	Vitronectin, fibrinogen, von Willebrand factor, laminin, thrombospondin, fibronectin
$\alpha_6\beta_4$	CD49f–CD104	Laminin
$\alpha_V\beta_5$		Vitronectin, fibronectin
$\alpha_V\beta_6$		Fibronectin
$\alpha_4\beta_7$		VCAM-1, MAdCAM-1, fibronectin
$\alpha_{\mathrm{IEL}}\beta_7$		
$\alpha_V\beta_8$		

gp, Glycoprotein; LFA, lymphocyte function-associated molecule; Mac, macrophage glycoprotein associated with complement receptor function; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; MAdCAM, mucosal addressin cell adhesion molecule

peripheral blood lymphocytes, while all three β_2 integrins, i.e. $\alpha_L\beta_2$, $\alpha_M\beta_2$ and $\alpha_X\beta_2$, can be found on neutrophils, monocytes and NK cells respectively[20]. The expression on the leucocyte surface of $\alpha_X\beta_2$ and, preferentially $\alpha_M\beta_2$ is increased under inflammatory conditions after stimulation with calcium ionophore, phorbol esters, formyl-methionyl-leucyl-phenylalanin (FMLP), granulocyte–macrophage colony-stimulating factor, C5a, tumour necrosis factor (TNF) α and leukotriene B_4[21]. The β_2 integrins bind to immunoglobulin-like proteins (intercellular adhesion molecules; ICAMs) on the surface of endothelial cells[20,22] and thereby mediate leucocyte–endothelial cell interaction[23–28]. Binding of β_2 integrins with ICAMs requires activation of the surface-resident integrins by stimuli, such as complement components, cytokines or lipid mediators. Additional ligands for the β_2 leucocyte integrins include soluble proteins, i.e. fibrinogen, factor X and complement fragments (*Table 1*)[20,29].

β_3 integrins. The β_3 subfamily of integrins consists of the platelet glycoprotein (gp) $\alpha_{\mathrm{IIb}}\beta_3$ complex and the vitronectin receptor $\alpha_V\beta_3$[11,30]. $\alpha_{\mathrm{IIb}}\beta_3$ is a calcium-dependent heterodimer on activated platelets, involved in platelet aggregation by binding to fibrinogen and (with lower affinity) to fibronectin, von Willebrand factor, vitronectin and thrombospondin[31]. Induction of $\alpha_{\mathrm{Hb}}\beta_3$ can be achieved by platelet interactions with C1q multimers, resulting in the activation of $\alpha_{\mathrm{IIb}}\beta_3$ fibrinogen binding sites and additional expression of P-selectin as well as platelet procoagulant activity, all of which is likely to contribute to thrombotic events associated with complement activation and inflammation[32]. The fact that there is a high degree of homology of $\alpha_{\mathrm{IIb}}\beta_3$ with the other integrins indicates that platelet aggregation and many of their interactions with the endothelium and the subendothelium may be considered within the broader context of cellular adhesion.

Integrins with other β subunits. At least five other β subunits have been described and characterized to varying degrees. On epithelial-type cells the β_4 subunit serves as an alternative to β_1 for the α_6 subunit[33] and binds to laminin. Besides β_1, the α_4 integrin can also associate with another β subunit, which was first called β_P[34] and which is now designated β_7[8]. The $\alpha_4\beta_7$ integrin is a cell-surface heterodimer, mostly expressed on leucocytes, which plays a major role in lymphocyte homing to intestinal tissue via adherence to the gut homing receptor mucosal addressin cell adhesion molecule (MAdCAM) 1[35]. $\alpha_4\beta_7$ also binds to fibronectin and VCAM-1[36–38], and recent *in vitro* and *in situ* studies have demonstrated the ability of $\alpha_4\beta_7$ to mediate selectin-independent contact and attachment of lymphocytes to MAdCAM-1, and of TK1 lymphoma cells to VCAM-1, under shear conditions[10]. Moreover, it has recently been shown that the α_4 chain can itself serve as a ligand for both $\alpha_4\beta_7$ and $\alpha_4\beta_1$[39].

Adhesion molecules of the immunoglobulin gene superfamily

The immunoglobulin gene superfamily encompasses a wide variety of cell-surface molecules characterized by an immunoglobulin homology unit. These proteins are involved in antigen recognition (C1 type: major histocompatibility antigens, CD4, CD8, T cell receptor), complement binding or cell adhesion (C2 type)[9]. Cell adhesion-mediating molecules include CD2, CD58 (lymphocyte function-associated molecule 3) and CD56 (also designated neural cell adhesion molecule; NCAM), as well as molecules that function in leucocyte trafficking, i.e. ICAM-1, ICAM-2 and ICAM-3, VCAM-1, platelet–endothelial cell adhesion molecule (PECAM) 1 and MAdCAM-1 (*Table 2*).

Intercellular adhesion molecules. ICAM-1 is a transmembrane glycoprotein which contains five immuno-

Table 2 Adhesion molecules of the immunoglobulin gene superfamily

Immunoglobulin	Other names	Ligand
ICAM-1	CD54	$\alpha_L\beta_2$ (CD11a–CD18) $\alpha_M\beta_2$ (CD11b–CD18)
ICAM-2	CD102	$\alpha_L\beta_2$ (CD11a–CD18)
ICAM-3	CD50	$\alpha_L\beta_2$ (CD11a–CD18) $\alpha_M\beta_2$ (CD11b–CD18)
VCAM-1	CD106	$\alpha_4\beta_1$ (CD49d–CD29) $\alpha_4\beta_7$
PECAM-1	CD31	PECAM-1
MAdCAM-1		L-selectin, $\alpha_4\beta_7$

ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; PECAM, platelet–endothelial cell adhesion molecule; MAdCAM, mucosal addressin cell adhesion molecule

globulin domains and is found on haematopoietic and non-haematopoietic cells[40]. On endothelial cells ICAM-1 is present only at low levels under normal (non-activated) conditions. However, it is dramatically upregulated after stimulation with interferon (IFN) γ, TNF-α, interleukin (IL) 1β and endotoxin (lipopolysaccharide; LPS). The expression and function of ICAM-1 on vascular endothelium is a characteristic feature of the inflammatory–immune response, mediating the process of leucocyte–endothelial cell interaction by binding to $\alpha_L\beta_2$ and $\alpha_M\beta_2$ integrins[41,42].

ICAM-2, which contains two extracellular immunoglobulin domains, is homologous to ICAM-1 and is constitutively expressed on endothelial cells, platelets, dendritic cells, monocytes and some lymphocytes. However, its expression is not modified by distinct inflammatory stimuli, and the molecule binds solely to $\alpha_L\beta_2$, but not to $\alpha_M\beta_2$, integrins[43,44].

ICAM-3, which contains five immunoglobulin domains, is closely related to ICAM-1[45] and is constitutively expressed on all leucocytes; it is expressed on endothelial cells only in disease states. ICAM-3 interacts with the $\alpha_L\beta_2$ integrin and is thought to regulate the $\alpha_L\beta_2$–ICAM-1 cell adhesion pathway[46].

Vascular cell adhesion molecules. VCAM-1 is a transmembrane protein and a member of the immunoglobulin gene superfamily. Initially the molecule was described as consisting of six extracellular immunoglobulin-like domains (6D VCAM-1)[47], but it is now known that 6D VCAM-1 arises from alternative splicing of a seven-domain form of VCAM-1 (7D VCAM-1)[9], the form that is predominantly expressed on activated human endothelial cells[48,49]. VCAM-1 is upregulated by TNF-α, IL-1 and LPS, and is involved in the adhesion of lymphocytes, monocytes and eosinophils to vascular endothelium through binding with its counter-receptors, the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins[10,12,50]. Because neutrophils do not express these integrins, they do not bind to VCAM-1.

Platelet–endothelial cell adhesion molecules. PECAM-1, which consists of six extracellular immunoglobulin-like domains, is structurally related to other cell–cell adhesion molecules, such as ICAM-1, VCAM-1, NCAM and carcinoembryonic antigen (CEA); it is expressed in large amounts on endothelial cells at intercellular junctions, on platelets and on some leucocytes[51–53]. The molecule is constitutively expressed on endothelial cells and expression is not modified by IFN-γ, TNF-α or IL-1[54]. PECAM-1 mediates adhesion through homophilic binding interactions and, since the molecule is concentrated at the intercellular junctions of endothelial cells, it is thought to play a major role in the maintenance of endothelial integrity and regulation of leucocyte transendothelial migration[50,55].

Mucosal addressin cell adhesion molecules. MAdCAM-1 is an immunoglobulin gene superfamily molecule for lymphocytes that is expressed by high endothelial venules in mucosal lymph nodes; it is involved in lymphocyte emigration into Peyer's patches and intestinal lamina propria[56,57]. The predicted extracellular domain of the addressin, which has structural homology with two other immunoglobulin-like proteins, ICAM-1 and VCAM-1, comprises three immunoglobulin-like domains[58]. The molecule is involved in tissue-specific homing of lymphocytes by mediating the adhesion of lymphocytes to venules of lymph nodes and mucosal lymphoid tissues via interaction with the $\alpha_4\beta_7$ integrin[10,35]. In addition, a subset of MAdCAM-1 has been reported to express the mouse endothelial cell antigen (MECA) 79 carbohydrate antigen and so to support cell–cell interaction by binding to L-selectin[35,59].

Neural cell adhesion molecules. The calcium-independent adhesion molecules, NCAM and neural adhesion molecule L1, both members of the immunoglobulin gene superfamily, are two of at least four well defined receptor systems in the neuronal membrane that mediate neurite outgrowth over a wide variety of neuronal substrata, such as glial cells (also over skeletal muscle)[60–62]. Besides neural cadherin (N-cadherin), NCAM and L1 potently induce neurite outgrowth via homophilic (self) binding mechanisms[63–65], although heterophilic partners have been described in certain cases, such as the axonin 1 (transiently expressed axonal surface glycoprotein; TAG-1) glycoprotein, which mediates neurite outgrowth by interaction with L1[66]. Analysis of the expression of these molecules during development may provide essential information on the role of cell–cell interaction during histogenesis.

Adhesion molecules of the cadherin superfamily

Cadherins are calcium-dependent single-pass transmembrane glycoproteins that function by means of homophilic interactions[67,68]. The molecules are characterized by an extracellular portion, usually consisting of five tandem repeat sequences, and a short cytoplasmic tail, interacting with the cytoskeleton via distinct proteins (catenins)[69]. The adhesive function of cadherins is primarily localized in the first amino-terminal domain and presents with a structure which is remarkably similar to that of the immunoglobulin gene superfamily[70]. All types of cells that form solid tissues express some members of the cadherin superfamily. As cadherins display homophilic binding they define adhesion specificities for the majority of cell types. Since cadherins also take part in other cell–cell interaction phenomena, i.e. the formation of junctional complexes and cell polarization, they are considered to be important regulators of morphogenesis[67].

Today, a wide group of related molecules with diverse functions are classified as members of the cadherin family. Four members are characterized at the molecular level; these are epithelial cadherin (uvomorulin, cell–CAM 120/80, Arc-1) (E-cadherin), neural cadherin (A-CAM, N-

Cal-CAM) (N-cadherin), placental cadherin (P-cadherin) and the liver cell adhesion molecules (L-CAMs)[67]. The overall homology between cadherins from different tissues and different species is between 50 and 60 per cent[3].

Epithelial cadherin. The expression of E-cadherin may be developmentally regulated since its switching on and off correlates with a variety of morphogenetic events that involve cell aggregation or disaggregation[71]. However, in the adult, almost all epithelia express the molecule, which tends to be distributed uniformly throughout the epithelial layer[3]. Since E-cadherin function is crucial for the maintenance of epithelial structure[72], alterations in function or loss of expression may be associated with loss of normal cell–cell integrity. The importance of the maintenance of adult epithelial structures suggests that this molecule not only plays a major role in the context of development but, in cases of dysfunction, is also involved in the process of epithelial cell tumour invasion[3].

Neural cadherin. N-cadherin is found primarily on neural tissues[67] but it has also been demonstrated in the lens of the eye, myocardium and skeletal muscle[67,73]. The molecule is expressed, like NCAM, in development and may contribute to neural induction and neuritogenesis[67]. This is supported by experimental studies demonstrating that N-cadherin, like NCAM and L1, promotes neurite outgrowth via a homophilic interaction with products of the same gene expressed in non-neuronal cells[65,74], and that perturbation of N-cadherin function can inhibit neurite regeneration over monolayers of astrocytes, muscle cells and Schwann cells[75]. However, N-cadherin may also function as a heterophilic receptor for products of distinct but related genes, such as R-cadherin[76]. Although both N-cadherin and NCAM are neural morphoregulatory molecules, their function may be distinctly different. N-cadherin requires, as do all members of the cadherin superfamily, Ca^{2+} for its adhesive function; NCAM does not. In addition, whereas NCAM-dependent neurite outgrowth is highly cooperative and exhibits a clear threshold effect[64], N-cadherin-dependent neurite outgrowth is essentially linear[65]. In the case of N-cadherin, but not of NCAM, overexpression early in development can result in malformation of the neural tube[77]. The function of N-cadherin in the adult may include the extension of axons from neurons in a precise manner to innervate their target tissue after injury. It may also include the preservation of structural cell–cell integrity, not only in neural tissue, as demonstrated by the maintenance of the structure of the intercalated discs between adjacent muscle cells[73].

Placental cadherin and others. P-cadherin is primarily expressed in placenta and epithelium, but it may also be transiently expressed in other tissues during development. In parallel with E-cadherin, P-cadherin is expressed in almost all epithelia in adults[78]. However, while E-cadherin is distributed uniformly throughout the epithelium, P-cadherin is located mainly at the more basal layers. It functions as an adhesion molecule by homophilic attraction to itself[79]. Beside E-, N- and P-cadherins, a considerable number of new members of the cadherin superfamily have been identified, including B-, M- (muscle), R-, T- (truncated), EP- (with homology to both E- and P-cadherin), XB- (xenopus blastomere) and U-cadherins; all the individual structural aspects and functions of these molecules are not yet clear[80].

Adhesion molecules of the selectin superfamily

In cases of injury, inflammation and distinct diseases, circulating leucocytes are recruited from intravascular compartments into tissue by specific leucocyte–endothelial cell interactions. The initial contact of leucocytes with the microvascular endothelium, i.e. leucocytes rolling along the endothelium, is mediated by adhesion molecules of the selectin superfamily. The family includes three closely related cell surface molecules: L-selectin (MEL-14, leucocyte adhesion molecule-1, lectin cell adhesion molecule-1, CD62L), expressed by leucocytes; E-selectin (endothelial leucocyte adhesion molecule-1, CD62E), expressed by vascular endothelium; and P-selectin (platelet activation-dependent granule-external membrane, platelet α-granule membrane protein-140, CD62P), expressed by both platelets and vascular endothelium[81,82]. Their extracellular region is characterized by an amino-terminal calcium-dependent lectin domain, an epidermal growth factor-like domain and two to nine short consensus repeat units, which are homologous to domains known from complement binding proteins[82]. The short consensus repeat domains have been suggested as determinants of ligand binding specificity, probably by serving as structural elements for individual presentation of the lectin and epidermal growth factor domains. Selectins bind to cell surfaces by carbohydrate recognition, specifically to sialyl Lewis^x or carbohydrates related to this structure[81,83].

L-selectin. L-selectin, characterized by two consensus repeats of the complement regulatory protein domains, is constitutively expressed on haematopoietic cells, including lymphocytes, neutrophils, monocytes, eosinophils, basophils and NK cells, and mediates binding to endothelium during capture and rolling, as well as lymphocyte binding during the homing process[84]. Several ligands have been identified, including at least three different heavily glycosylated mucin-like proteins: CD34, glycosylation dependent cell adhesion molecule-1 and MAdCAM-1[85–87]. Other ligands, in particular carbohydrate-based inducible molecules on activated vascular endothelium, have been proposed[82], but their identity remains to be defined. Although leucocyte–endothelial cell interactions may involve several members of the selectin superfamily in normal and distinct pathological conditions, *in vivo* studies have demonstrated that L-selectin can mediate leucocyte rolling independently of E- or P-selectin[88]. It is noteworthy that cellular activation results in reversible loss of L-selectin expression by endoproteolytic release of the receptor from the cell surface, with a concomitant increase of expression of other adhesion receptors, which mediate firm attachment to endothelial cells[89], and considerable amounts of soluble circulating L-selectin, which probably modulate further leucocyte adhesion characteristics[90].

E-selectin. E-selectin is characterized by a C-type lectin-like binding domain, the epidermal growth factor-like domain and six complement regulatory protein regions[9]. E-selectin production and expression on endothelial cells is rapidly (4–6 h) induced after activation by a variety of inflammatory mediators, including TNF-α, IL-1, INF-γ and LPS[82]. E-selectin binds to the 150 000-Da glycoprotein E-selectin ligand 1[91]; however, it may also bind to a ligand termed P-selectin glycoprotein ligand (PSGL) 1[92]. Relevant function of E-selectin pertains to various inflammatory conditions[93] characterized by broad expression of both E-selectin in the vasculature and the soluble form of E-selectin in serum[82,90].

P-selectin. P-selectin has nine consensus repeats of the complement regulatory protein regions and is constitutively stored in Weibel–Palade bodies of endothelial cells and in the α granules of platelets[9]. After appropriate activation with agents, such as thrombin, histamine, complement, oxygen radicals and cytokines, the molecule is rapidly (within minutes) mobilized to the external plasma membrane[82]. P-selectin binds to PSGL-1[92,94] and mediates leucocyte rolling under physiological and pathophysiological conditions[95–97]. The *in vivo* function of P-selectin, i.e. the induction of leucocyte rolling and subsequent extravasation, has been elegantly confirmed by experimental studies in P-selectin-deficient mice which have demonstrated by intravital microscopy a virtually total absence of leucocyte rolling in mesenteric venules[98]. In addition, a functionally active soluble plasma P-selectin may modulate leucocyte adhesion to P-selectin expressed on endothelial cells[90,99].

Other cell adhesion molecules

With the identification of GlyCAM-1, MAdCAM-1, PSGL-1 and CD34 as ligands for individual selectins, an additional family of adhesion molecules, the sialomucins, has been proposed[86,87]. As these molecules provide an extended structure which exposes multiple terminal sugars (and in case of MAdCAM-1 also contains immunoglobulin-like regions), members of this family may serve multiple adhesion functions[9].

A variety of other molecules have also been demonstrated to induce and modulate cell–cell adhesion, including iC3b, fixed to the endothelial surface and binding to CD11b–CD18[100]; fibrinogen, acting as a soluble ligand which promotes leucocyte–endothelial cell interactions by 'bridging' the binding of CD11b–CD18 and ICAM-1[101]; and the extracellular matrix protein fibronectin with its CS (connecting segment) 1 segment, which is recognized by the $\alpha_4\beta_1$ integrin (VLA (very late antigen) 4)[102]. Moreover, additional putative endothelial adhesion molecules, such as vascular adhesion protein 1 and lymphocyte–vascular adhesion protein 2, have been suggested as novel adhesion molecules involved in lymphocyte adherence to endothelium[103,104].

Adhesion molecules in surgical pathophysiology

Concomitant with the identification of specific adhesion molecules, many diseases have been shown to be associated with a lack, or dysfunction, of distinct receptors; the opposite is also possible – overexpression of distinct receptors. The crucial role of lack or dysfunction of adhesion molecules is best illustrated by the two hereditary syndromes, designated leucocyte adhesion deficiency types 1 and 2, which are determined by diminished expression of CD18[105] and sialyl Lewis^{x}[106] respectively. These syndromes are characterized by frequent and overwhelming infections due to the inability of neutrophils to infiltrate pathogen-bearing tissues[50]. In contrast, a large array of acquired or genetically codetermined diseases involving the immune system are associated with upregulation or overexpression of individual adhesion molecules. These diseases include glomerulonephritis, encephalomyelitis, arthritis, different types of vasculitis (polyarteritis nodosa, Kawasaki disease, Wegener's granulomatosis), asthma, inflammatory disease of the liver (viral hepatitis B, alcoholic hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis) and inflammatory disease of the skin (psoriasis, atopic dermatitis, scleroderma, erythema multiforme, lupus erythematosus). These conditions demonstrate differential patterns of increased expression of E-selectin, ICAM-1 and VCAM-1. The significant role of these adhesion molecules has been underlined by a large number of studies, which have demonstrated successful treatment in experimental models by the use of corresponding monoclonal antibodies specifically directed against the individual molecules[50,107].

Surgeons may not often be faced with the above diseases, but there exists also a variety of pathological conditions, more apparent in the field of surgery and intensive care medicine, which are associated with specific function or dysfunction of adhesion molecules. These are: (i) inflammatory processes, such as peritonitis, pancreatitis and sepsis, as well as specific inflammatory diseases (ulcerative colitis or Crohn's colitis); (ii) ischaemia–reperfusion and shock–resuscitation; (iii) transplantation and rejection; (iv) dysfunctions in angiogenesis and wound healing; (v) arteriosclerosis and thrombosis; and (vi) tumour formation and metastasis.

Inflammation and sepsis

Localized and systemic inflammatory processes are characterized by the liberation of inflammatory mediators (cytokines, arachidonic acid metabolites, oxygen radicals, etc.), which, together with bacterial components (LPS), activate both leucocytes and endothelial cells. Leucocytes mediate inflammation-induced tissue injury[95]; the recruitment into tissue is dependent on a multistep process involving the sequential engagement of adhesion molecules, which include selectins with their corresponding ligands for primary leucocyte–endothelial cell interaction and the family of β_2 integrins which react with endothelial ICAMs to cause a secondary leucocyte–endothelial cell interaction[108]. In this scheme selectin-mediated rolling of leucocytes along the endothelial lining of the microvasculature (primary leucocyte–endothelial cell interaction) is a prerequisite for later firm attachment (secondary leucocyte–endothelial interaction) and subsequent transendothelial migration[109].

In line with this, intravital microscopic studies have demonstrated that inflammation, in particular the exposure of LPS to tissue, is associated with a microvascular accumulation of leucocytes due to leucocyte rolling and adhesion; this is encountered preferentially in postcapillary venules[110]. Analysis of potential molecular determinants for LPS-induced leucocyte rolling has demonstrated massive synthesis of E- and P-selectin messenger RNA (mRNA)[111], with the consequence of increased expression of these molecules on endothelial cells[112,113]. Moreover, there is evidence that endotoxaemic injury is mediated by the molecular mechanisms of leucocytic firm attachment to endothelial cells, since LPS induces upregulation of leucocytic β_2 integrins and endothelial ICAMs[114], and monoclonal antibodies directed against CD11b–CD18 (but not CD11a–CD18) and ICAM-1 are effective in reducing LPS toxicity to tissue[114–116].

However, although the blockade of ICAM-1 may attenuate LPS-induced tissue injury[114], it does not necessarily inhibit leucocyte accumulation within the microvasculature. Recent studies indicate that initial LPS-induced microvascular leucocyte adhesion is not affected by blockade of ICAM[117,118], which is in accordance with observations in ICAM-1-deficient mice demonstrating no influence on initial LPS-induced neutrophil accumulation in tissue, but significant reduction of lethality[119]. These results suggest alternative molecular pathways of LPS-induced leucocyte adhesion, and differential impact on the manifestation of tissue injury and organ dysfunction.

Non-specific local inflammatory processes, such as peritonitis, show a similar engagement of adhesion molecules involved in local leucocyte recruitment, including PECAM-1 (CD31) function for transendothelial migration[120]. Moreover, peritonitis induces a generalized (systemic) inflammation, which is reflected by increased adhesion molecule expression (E-selectin) at sites distinct from the peritoneal cavity[121]. Other local inflammatory processes which include an autoimmune pathogenesis may also involve various types of adhesion molecules at the site of inflammation. In patients with ulcerative colitis and Crohn's disease recent studies indicate genetic variations of the functionally important domain III of ICAM-1[122]. In a primate model of spontaneous colitis, marked by periodic flares of acute inflammation that closely mimics human ulcerative colitis, the expression of both E-selectin and VCAM-1 was found to be significantly increased[123]. The fact that significant reduction of colitis activity was observed with monoclonal antibodies to $\alpha_4\beta_1$ (counter-receptor for VCAM-1), but not to E-selectin[123], indicates a pivotal role of $\alpha_4\beta_1$–VCAM-1 communication in the manifestation of disease.

Ischaemia–reperfusion and shock–resuscitation

There has been growing recognition that leucocyte activation, adhesion and transmigration are key components in the pathophysiology of ischaemia–reperfusion- and shock–resuscitation-induced disorders, which have previously not been regarded as 'inflammatory' diseases. Apart from the failure to re-establish nutritive perfusion (capillary no-reflow)[124,125], the reperfusion- and resuscitation-associated leucocytic inflammatory response (reflow paradox)[126] contribute to the manifestation of microvascular and tissue injury after ischaemia and low-flow states[127–130]. This view is strongly supported by experiments demonstrating that neutrophil depletion effectively prevents tissue injury after both ischaemia and haemorrhagic shock[131,132].

The impact of distinct adhesion molecules, including the leucocytic β_2 integrin CDIIb–CD18 and the endothelial ICAM-1, in mediating postischaemic tissue injury was indirectly evidenced in experimental studies by blockade of these molecules with monoclonal antibodies; this demonstrated a significant reduction in cellular injury and an improvement in organ function and survival[133–136]. In fact, a large number of intravital microscopic studies have now precisely analysed the kinetics of leucocyte–endothelial cell communication, including leucocyte rolling, adhesion and transendothelial migration. These have demonstrated, by the *in vivo* blockade of selectins[137] and the $\alpha_M\beta_2$ integrin CDIIb–CD18[138] and ICAM-1[138,139], profound attenuation of leucocyte adhesion and, consequently, abrogation of microvascular and tissue injury. These studies clearly demonstrate that adhesion molecule-mediated leucocyte accumulation takes place primarily in the postcapillary venular segments[138,139], while stasis of leucocytes in capillaries may be a process dependent solely on perfusion pressure[140] and alterations in morphological and mechanical properties of leucocytes and endothelial cells[129,139], rather than on the function of adhesion molecules[139].

In venules, however, the multistep sequence of adhesion molecule-mediated leucocyte–endothelial cell communication seems also to be preserved in ischaemia–reperfusion, since the blockade of selectin-mediated leucocyte rolling, which is suggested as the prerequisite for firm attachment, not only prevents rolling (primary leucocyte–endothelial cell interaction), but also effectively abrogates the secondary adhesion processes[137]. Moreover, *in vivo* studies in postischaemic liver[139] demonstrate that blockade of secondary leucocyte–endothelial cell interactions by a monoclonal antibody to ICAM-1 also attenuates primary interactions, i.e. leucocyte rolling, which may be explained by the fact that firmly adherent leucocytes, probably by the release of oxygen radicals, recruit other leucocytes by induction of selectin-mediated primary interactions[141,142]. The interruption of this vicious circle may therefore be an effective approach for preventing leucocyte-mediated postischaemic tissue injury[143].

Transplantation and rejection

Early development of tissue injury and organ dysfunction after transplantation may represent a manifestation of ischaemia–reperfusion injury. *In vivo* studies have demonstrated that post-transplant leucocyte–endothelial cell interactions and manifestation of tissue injury depend both on the cold ischaemia time period[144] and the individual compounds in the preservation and rinse solutions[145,146]. Early adhesion molecule-dependent leucocyte adherence after transplantation[147] is probably mediated by reactive oxygen metabolites, because radical scavengers effectively block these cell–cell interactions and, concomitantly, attenuate tissue injury[144–146]. In addition to direct ischaemia–reperfusion-induced injury, oxygen radical-mediated postischaemic leucocyte–endothelial cell interactions may trigger the manifestation of transplant rejection. This view is supported by clinical reports demonstrating profound attenuation of both acute and chronic kidney rejection after a single application of superoxide dismutase during the early post-transplant period[148].

Indeed, there is increasing evidence that adhesion molecules are involved in the process of graft rejection[149,150]. A variety of studies have shown overexpression of distinct adhesion molecules during the rejection process of cardiac[151–153], hepatic[154,155], renal[156–158], pancreatic [155] and small bowel transplants[159], involving P- and E-selectin as well as ICAM-1 and VCAM-1. Nakakura *et al.*[160] have suggested that blockade of adhesion molecules may prevent sensitization to alloantigens and so prolong graft survival. The participation of cellular interactions, via ICAM-1 and VCAM-1 with their counter-receptors $\alpha_L\beta_2$ and $\alpha_4\beta_1$, in the process of graft rejection was confirmed by experimental *in vivo* studies; monoclonal antibodies directed against these molecules caused attenuation of graft rejection with prolongation of allograft[161–163] and xenograft[164,165] survival. Similar results have recently been reported with gene-targeted animals deficient in the expression of specific adhesion molecules[166] and with antisense oligonucleotides[167]. Moreover, initial clinical trials have now demonstrated that blockade of distinct adhesion molecules, such as $\alpha_L\beta_2$ integrins and ICAM-1, is effective in preventing kidney graft rejection[168,169]. Taking the view that T cell anergy or an antigen-specific unresponsiveness is induced specifically by blocking the interaction of adhesion molecules with their ligands, immunosuppression with antibodies to ICAM-1 and/or $\alpha_L\beta_2$ integrins may be better than conventional (relatively unspecific) transplant immunosuppressive regimens.

Angiogenesis and wound healing

Endothelial adhesion molecules facilitate the entry of leucocytes into inflamed tissue, which, in turn, promotes angiogenesis and neovascularization, processes central to the initiation and progression of wound repair[170]. In response to angiogenic stimuli, endothelial cells adopt a migratory phenotype associated with alterations of expression of many proteins, including proteases, growth factors, adhesion molecules and other cell surface receptors. The role of adhesion molecules in the process of angiogenesis is not yet completely understood. Gamble *et al.*[171] have demonstrated *in vitro* that blockade of the integrins $\alpha_2\beta_1$ and $\alpha_V\beta_3$ by monoclonal antibodies promotes capillary tube formation, while others have identified the $\alpha_V\beta_3$ integrin as a marker of angiogenic vascular tissue in wound granulation[172]. Moreover, previous *in vitro* studies have demonstrated inhibition of capillary formation by antibodies directed against E-selectin[173], and recent *in vivo* studies have confirmed the crucial role of both soluble E-selectin and soluble VCAM-1 as mediators of angiogenesis[174]. The mechanism of action may be the shedding of these molecules when activated leucocytes bind to endothelial cells and release cytokines, with the result that the shed molecules bind adjacent endothelial cells via their respective ligands, sialyl Lewis^x and $\alpha_4\beta_1$, and thereby exert a direct angiogenic effect on these endothelial cells[174]. In fact, sialyl Lewis^x and sialyl Lewis^a have been shown to participate in the process of angiogenesis and vascularization[173]. This supports the hypothesis of a link between cellular adhesion and angiogenesis.

The process of wound healing is a complex interplay between the action of mediators, cellular function and molecular communication. After tissue damage platelets may bind to exposed matrix via β_1 and β_3 integrins, and further platelet aggregation may be promoted[11] by thrombin-induced activation of platelet $\alpha_{IIb}\beta_3$. Platelets, fibrinogen, fibrin and fibronectin form a provisional wound matrix, and platelet granule contents, thrombin and tissue factors may initiate an inflammatory reaction with endothelial and white blood cell activation, adhesion and release of cytokines. These then stimulate the upregulation of integrins on macrophages and fibroblasts, which promotes their migration into the wound site[11].

Apart from angiogenesis and matrix formation, keratinocyte migration is an essential event in the process of cutaneous wound healing, which probably involves additional cellular interactions via distinct adhesion molecules. In normal skin tissue keratinocytes reside on the basement membrane, composed primarily of laminin and type IV collagen, and express a variety of integrins along their lateral borders[175]. During wound healing they become activated and migratory, which is associated with increased expression of ICAM-1, α_V subunits and $\alpha_5\beta_1$ integrins (fibronectin receptor)[175,176]. Expression of these molecules disappears successively when a new basement membrane is formed and epithelial integrity is achieved. Further studies must elucidate specific dysfunction of the individual molecules in conditions of impaired wound healing, e.g. in diabetic or ischaemic disease.

Arteriosclerosis and thrombosis

Development of arteriosclerosis involves the processes of inflammation, intimal accumulation of macrophages, smooth muscle cell migration and proliferation, and extracellular matrix deposition[177], which in turn require the function of adhesion molecules. Manifestation of atherosclerotic lesions is preceded by mononuclear leucocyte adhesion to the vascular endothelium and migration into the intima. This is supported by *in vitro* studies demonstrating that oxidized low density lipoprotein (LDL), a substance associated with atherosclerosis, acts on leucocytes and endothelial cells to enhance adhesion[178]. *In vivo* studies have confirmed that oxidized LDL induces leucocyte–endothelial cell interactions and that these interactions are mediated by receptors for platelet-activating factor[179], but also involve the leucocytic CD11b–CD18 adhesion receptor complex[180]. On endothelial cells, atherogenic lipoproteins and lipid-rich diets induce VCAM-1 and ICAM-1 expression *in vitro*[181], and VCAM-1 expression at sites of monocyte infiltration *in vivo*[182,183]. In parallel, the pattern of adhesion molecule expression in human atherosclerotic lesions is characterized by the induction of E-selectin on arterial endothelium, and ICAM-1 on endothelium, mononuclear leucocytes and smooth muscle cells[184–186].

Although development of atherosclerotic lesions with formation of foam cells by immigrating mononuclear leucocytes may require the upregulation of both leucocytic and endothelial adhesion molecules, progression of those lesions may include selective loss or downregulation of cell-surface adhesion receptor expression. In early stages of atherosclerosis, foam cells have been noted to re-enter the circulation, a 'clearance system', which was interpreted as a defence mechanism against atherosclerosis[187]. In advanced lesions, locomotion and re-entry into the circulation of lipid-laden macrophages may be inhibited by lack of adhesion molecule function. This view is supported by a recent study which demonstrated downregulation of CD11b and CD18 expression in atherosclerotic lesion-derived macrophages[188]. This underlines the complex interplay of cellular and molecular mechanisms in the development and progression of atherosclerosis.

In the current state of knowledge of the multicellular process of thrombosis, it is probably more accurate to view platelet aggregation and binding to fibrinogen, neutrophils and monocytes as a cell adhesion event. Recent studies show that this process involves β_1 and β_3 integrins, P-selectin, the $\alpha_V\beta_3$ vitronectin receptor and thrombospondin[189–191]. *In vitro* experiments demonstrate that the activation of platelets is associated with activation of $\alpha_5\beta_1$ (gpIc–IIa) and $\alpha_{IIb}\beta_3$ (gpIIb–IIIa) complexes, which support fibrinogen and fibronectin binding[32,192]. Antibodies directed against these glycoprotein complexes or RGD (Arg-gly-Asp) peptides showed effective inhibition of platelet aggregation and adhesion both *in vitro*[192] and *in vivo*[193,194], and so may represent a new therapeutic approach in the prevention or treatment of thrombosis. This may be of particular interest in specific diseases, e.g. insulin-dependent diabetes mellitus, which are characterized by an enhanced intravascular platelet activation status with increased P-selectin, thrombospondin and $\alpha_{IIb}\beta_3$ platelet levels[195].

Tumour progression and metastasis

The complex processes of tumour progression and metastasis involve several steps including: (i) tumour growth and release of neoplastic cells; (ii) migration into the lymphatics or microvasculature; (iii) interaction with individual blood cells, i.e. platelets and leucocytes; (iv) adhesion to lymphatic or vascular endothelium at distant sites; (v) migration into parenchyma; and (vi) growth of tumour at the metastatic site[3]. There is ample evidence that adhesion plays a dual role in tumour progression–invasiveness and metastasis, and that molecules mediating these adhesion events essentially contribute to the aforementioned multistep cascade.

The initial step of cancer metastasis is the detachment of cells from the primary tumour mass, which may serve as an indicator of metastatic activity[67]. Indeed, under normal conditions with sufficient activity of cadherins, cells are unable to disrupt their mutual connections; only in the state of cadherin inactivation may cells be freed from their adhesive constraints and migrate out of their parent colonies. In fact reduced E-cadherin immunoreactivity, probably related to allelic loss or frequent somatic allelic inactivation of the E-cadherin gene[196], has been observed in a broad range of malignancies, including cancers of the head and neck, lung, breast, prostate, oesophagus, stomach and colorectum[197]. Clinical studies suggest that the loss of E-cadherin function is directly associated with tumour invasion and metastasis. In gastric carcinoma, highly differentiated tumours generally maintain homogeneous, strong expression of E-cadherin, while in poorly differentiated invasive tumours cadherin expression is found to be altered or even completely suppressed[67]. Moreover, in basal cell carcinoma, superficial tumours are characterized by normal expression of both P- and E-cadherin, while infiltrative carcinoma shows preservation of P-cadherin expression but severe reduction in that of E-cadherin[198]. Indeed, the loss of E-cadherin expression may serve as an indicator for prognosis in patients with malignancy. In colorectal cancer the level of expression of E-cadherin mRNA strongly correlates with clinical outcome: patients surviving 5 years or longer exhibit significantly higher levels of E-cadherin mRNA than those surviving less than 5 years[199].

During dissemination of neoplasms, adhesion to the vessel wall, which is essential for metastatic cells to arrest at distant sites, may involve the same endothelial cell-surface receptors used by leucocytes, i.e. selectins, sialyl Lewis^x and ICAM-1. E-selectin has been demonstrated to mediate dynamic interactions of breast and colonic cancer cells with endothelial cell monolayers[200]. The expression of this molecule is found to be increased on endothelial cells of small vessels adjacent to primary colorectal tumours; this is particularly the case in their metastatic lesions[102]. Moreover, the levels of serum E-selectin are found to be significantly raised in patients with hepatic metastasis compared with non-metastatic controls[201]. In malignant melanoma, expression of both E-selectin and P-selectin as well as $\alpha_4\beta_1$ integrins is negatively associated with the length of the disease-free interval, suggesting a crucial role for these molecules in the development of metastasis[202]. In the process of tumour progression and spreading, selectins may bind to sialyl Lewis X/A moieties, which have been shown to be expressed in both melanoma and colorectal cancer[203,204].

Apart from selectins, cell adhesion molecules of the immunoglobulin supergene family may play a determinant role in malignant transformation and progression to metastatic disease. This includes CEA in colorectal cancer and ICAM-1 in cutaneous melanoma and renal cell carcinoma[205,206]. The significance of ICAM-1 on tumour activity has been underlined by experiments demonstrating prevention of tumour growth by anti-ICAM-1 monoclonal antibody in the ARH-77 tumour model in SCID mice[207]. Function of adhesion molecules, however, may not only promote tumour progression and metastasis, but may also be involved in mediating cytotoxic immune response. Analysis of VCAM-1, which is a potential endothelial ligand for cytotoxic effector lymphocytes, has shown repressed expression by melanoma and carcinoma[208], indicating that the tumour may escape host defence by interfering with the mechanisms of effector cell extravasation.

The relationship of individual integrin expression and tumour progression appears to be complex probably because integrins may be required not only for tumour cell migration and adherence (tumour progression), but also for the immigration of cytotoxic effector cells (tumour regression). Analysis of adhesion molecules of the integrin superfamily on lymphocytes immigrating into metastatic tissue indicates no specific expression of individual β_1 and β_2 integrins, including $\alpha_2\beta_1$, $\alpha_4\beta_1$, $\alpha_6\beta_1$, $\alpha_L\beta_2$, $\alpha_M\beta_2$ and $\alpha_X\beta_2$[209], while analysis of integrins in tumour tissue is characterized by the loss of $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_V\beta_1$ and $\alpha_V\beta_5$ in breast cancer[210] and $\alpha_6\beta_1$ and $\alpha_V\beta_5$ in cutaneous melanocytic tumours[211,212]. In contrast, induced expression of integrins of the cytoadhesion family (β_3 integrins), involving both $\alpha_{IIb}\beta_3$[213,214] and $\alpha_V\beta_3$[212], has been demonstrated in malignant melanoma and various other tumours. The role of β_3 integrins in tumour progression is supported by experiments which demonstrate that $\alpha_V\beta_3$ integrin antagonists promote tumour regression by inducing apoptosis of angiogenic blood vessels[215], and that the blockade of $\alpha_{IIb}\beta_3$ inhibits tumour adhesion *in vitro* and metastasis *in vivo*[214]. Moreover, there is ample evidence that, besides these cytoadhesive molecules, platelets, thrombin, fibronectin, thrombospondin and von Willebrand factor are also involved in this promotion of tumour progression and metastasis[214,216–218].

Surgical intervention and techniques

Surgery is known to induce an inflammatory response which is characterized by leucocytosis and release of inflammatory mediators[219]. Laparotomy and exteriorization of the small intestine alone induces recruitment of leucocytes and adhesion molecule-mediated rolling and adherence to the endothelial lining of postcapillary segments (venules) of the mesentery[220]. Indeed, reduction of operative trauma by the use of a laparoscope for gastrointestinal surgery is associated with reduced liberation of inflammatory mediators, such as IL-6, and so may minimize the leucocytic response to surgery[219].

In situations involving the use of foreign material in surgery, e.g. cardiopulmonary bypass, vascular prosthesis and aortic valve replacement, increased adhesion molecule expression (β_2 integrins) may serve as a marker of neutrophil activation. This may be predictive of an ongoing inflammatory process that is linked to pulmonary dysfunction[221].

Conclusions

Modern methods in cell and molecular biology within the past few years have provided a plethora of clues to help in our understanding of the complex biological events involved in cellular communication. The use of sophisticated intravital techniques has allowed a bridge from *in vitro* observations to their potential relevance *in vivo*. They have permitted an understanding of complex biological interactions and disease mechanisms, and the development and testing of novel prophylactic and therapeutic approaches[222]. Cell-surface adhesion molecules, which mediate cellular communications, have been demonstrated to play an essential role in the pathophysiology of disease, including sepsis, ischaemia–reperfusion, transplant rejection, arteriosclerosis and thrombosis, and tumour progression and metastasis. The understanding of these molecular mechanisms which initiate tissue injury and organ dysfunction is vital to the art and science of surgery. Such knowledge may allow new therapeutic regimens to improve the care of surgical patients.

Assessment of the cellular expression of adhesion molecules, or measurements of individual levels of soluble receptors, may facilitate diagnosis and increase prognostic accuracy. For example, in malignant melanoma the expression of both E- and P-selectin, as well as $\alpha_4\beta_1$ integrins, is negatively associated with the length of the disease-free interval, suggesting that screening of these molecules should help in defining the subgroup of patients with melanoma at risk of developing metastasis[202]. Furthermore, the serum level of E-selectin in patients with colorectal cancer may provide useful information in the diagnosis of hepatic metastasis[201]; the level of expression of E-cadherin mRNA in such tumours may determine clinical outcome[199]. Similarly in transplantation, levels of soluble circulating adhesion molecules (E-selectin, VCAM-1 and ICAM-1) in serum[223] and, in particular, in bile[223,224] and urine[225], as well as the inducible tissue expression of these molecules[151,156,226], have been proposed as early predictive markers of acute rejection. They have the ability to differentiate between infection and rejection[223], and monitoring the decrease in the levels of these molecules may be indicative of successful antirejection therapy[226].

The knowledge of which adhesion molecules are involved in the distinct pathophysiology of disease opens the door to novel therapeutic strategies using monoclonal antibodies, antisense oligonucleotides and single gene products[227]. Experimental studies with anti-ICAM-1 antibodies have demonstrated inhibition of human tumour growth[207], protection from ischaemia–reperfusion injury[139] and prevention of allograft rejection in non-human primates[228]. The first clinical experience was reported in a phase I trial of immunosuppression with anti-ICAM-1 in renal allograft recipients; protection was achieved against delayed graft function and rejection[168].

From present knowledge of adhesion molecules and new anticipated discoveries[229], it seems highly likely that modulation of adhesion molecule function will become more widely used in the near future in the treatment of surgical patients.

Acknowledgements

This paper is dedicated to Professor Gernot Feifel in honour of his 60th birthday.

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British Journal of Surgery 1996, 83, 602–607

Review

Spontaneous rupture of hepatocellular carcinoma

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Spontaneous rupture of hepatocellular carcinoma (HCC) is a life-threatening condition; the mechanism is not clear but it is suggested that rupture is usually preceded by rapid expansion of the tumour secondary to bleeding from within its substance. Diagnosis may be made by abdominal paracentesis, ultrasonography, computed tomography or angiography; the positive rates of diagnosis are 86, 66, 100 and 20 per cent respectively. Prognosis is poor. Based on treatment results reported in the literature, the mean survival time for patients who underwent hepatectomy, transcatheter arterial embolization (TAE) and conservative therapy were 247, 98 and 13 days respectively. Judging from the reported results the first choice for emergency treatment of haemostasis is TAE. If laparotomy is undertaken, hepatic artery ligation, preferably of the branch supplying the liver lobe bearing the tumour, should be considered, together with haemostasis of the rupture site by various means (suture plication, packing, argon beam coagulation, use of microwave or absolute ethanol). Emergency hepatectomy should be reserved for patients with an easily resectable lesion who are in a stable cardiovascular condition. Conservative therapy may be used for selected patients in extremely poor condition. The rational treatment for the majority of patients with ruptured HCC is TAE, followed by hepatectomy if the lesion is resectable.

Spontaneous rupture of hepatocellular carcinoma (HCC) is a life-threatening condition. It accounts for 10 per cent of deaths from HCC in Japan[1]. About 12–14·5 per cent of patients with HCC are reported to develop this complication in Asia and Africa where the incidence of this cancer is high[2,3]. In recent years the incidence of rupture has been lower, probably due to a higher proportion of tumours being diagnosed at an early stage[4]. Accurate clinical diagnosis of spontaneous rupture of HCC is not easy. The prognosis remains poor and therapy is far from effective. The current status of knowledge about mechanism of rupture, diagnosis and therapy is discussed below.

Mechanism

Until now the mechanism of spontaneous rupture of HCC has been speculative (*Fig. 1*). The site of bleeding within the tumour is also speculative. Some investigators have considered that bleeding occurs from rupture of a parasitic artery or vein (such as the inferior phrenic vessels) feeding or draining the tumour[5] (*Fig. 2*). Some believe that bleeding comes from laceration of a superficial tumour secondary to trauma, either from outside[6,7] or from within as a result of repeated respiratory movement, especially for a tumour located under the diaphragm[3]. Hermann and David[8] observed that it was not the tumour that ruptured, but rather the overlying normal liver tissue which split from the pressure of expanding tumour growth. However, in the majority of cases bleeding is probably initiated within the tumour[3]. This leads to a sudden increase in pressure within the tumour followed by bursting through the tumour surface (*Fig. 3*). Thus ruptured HCC tends to occur in patients with carcinoma located at the periphery, protruding into

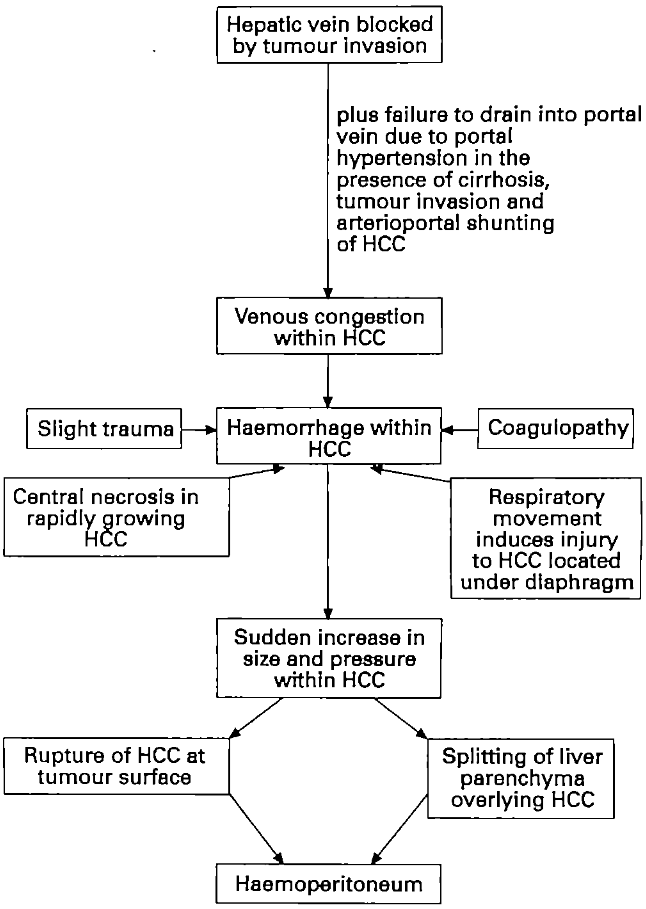
Hepatic vein blocked by tumour invasion
plus failure to drain into portal vein due to portal hypertension in the presence of cirrhosis, tumour invasion and arterioportal shunting of HCC
Venous congestion within HCC
Slight trauma
Haemorrhage within HCC
Coagulopathy
Central necrosis in rapidly growing HCC
Respiratory movement induces injury to HCC located under diaphragm
Sudden increase in size and pressure within HCC
Rupture of HCC at tumour surface
Splitting of liver parenchyma overlying HCC
Haemoperitoneum

Fig. 1 Possible mechanism of spontaneous rupture of hepatocellular carcinoma (HCC)

Paper accepted 22 November 1995

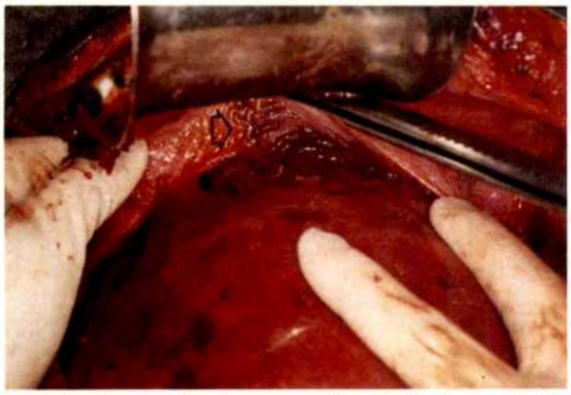

Fig. 2 Dilated parasitic veins (arrow) in the diaphragm draining a hepatocellular carcinoma

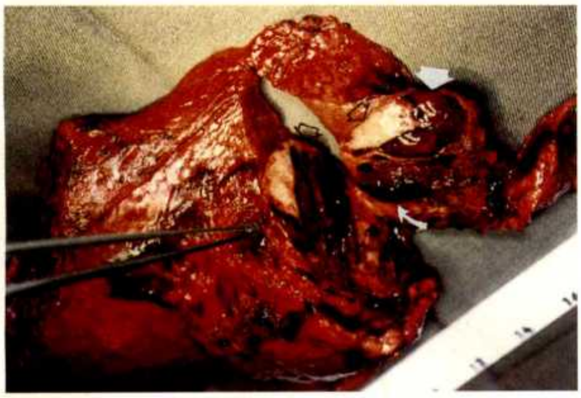

Fig. 3 Section of a ruptured hepatocellular carcinoma showing the tumour (open arrows), old blood clot (curved white arrow) and fresh blood clot (short white arrow) bursting through the tumour surface (as indicated by forceps)

the abdominal cavity and devoid of overlying normal liver parenchyma[5]. Spontaneous rupture tends to occur in large tumours[5], but small lesions located at the surface of liver also bleed and rupture[2,9].

Factors that initiate bleeding within the tumour are not known. Oral contraceptives are known to increase the vascularity of adenomas and HCC, and so the chance of bleeding[10,11], but the majority of ruptured tumours occur in men with underlying cirrhosis[3,12]. Rapidly growing tumour with necrosis in the centre may predispose the neovasculature of the HCC to rupture. However, transcatheter arterial embolization (TAE), which is a popular method of treatment of non-ruptured HCC, does not lead to a higher incidence of bleeding and rupture. Coagulopathy has been postulated as responsible for the initiation of spontaneous bleeding within the tumour[3], but spontaneous rupture does not occur in many patients with terminal HCC and liver failure. A more convincing hypothesis is that the pressure within the tumour increases when the branches of the hepatic veins are blocked, as the cancer invades into them[2,3] (*Fig. 1*). The venous blood in the tumour may drain into the subcapsular collaterals[2] or into the portal vein[2]. Drainage to the portal vein may be inefficient, however, when there is portal hypertension due to cirrhosis, tumour occlusion of the portal vein or arterioportal venous shunting[13]. Congestion within the tumour, therefore, rapidly increases, and bleeding and rupture occur when hepatic vein occlusion is complete[2,3,13]. This hypothesis has some support in that cirrhosis was found in almost all cases of ruptured HCC in two series[3,14], but evidence of concomitant hepatic vein obstruction was not available in these reports. Moreover, spontaneous rupture of HCC occurred in patients with normal livers in almost one-quarter to one-half of instances in other series[4,15]. In short, conclusive evidence for the hypothesis is lacking; detailed pathological studies comparing features of ruptured HCC and those of non-ruptured tumours are needed.

Diagnosis

The clinical diagnosis of ruptured HCC may not be easy because there are no specific symptoms. In some cases the presenting symptoms are not dramatic and may be indistinguishable from those of uncomplicated HCC[3]. Misdiagnosis on clinical grounds has been reported in 50 per cent of patients[16]; occasionally diagnosis of ruptured HCC is not made until laparotomy or autopsy[17]. The following features are helpful in making an early diagnosis:

1 The typical presentation is sudden epigastric or right hypochondriac pain which is present in 34 per cent of cases[1,16]. It may be associated with fainting or abdominal distension. In some situations HCC or chronic liver disease may have been diagnosed previously but, frequently, epigastric pain is the first symptom heralding the presence of carcinoma[16]. Middle-aged men are often affected by such a complication[18]. Some patients may have a history of minor blunt abdominal trauma[6,7].

2 Shock is present in 59–90 per cent of patients on admission[2,14], and 60–100 per cent have signs of peritonitis and/or abdominal distension[2,4].

3 Blood-stained ascites exists in all cases[19] and abdominal paracentesis is positive in about 86 per cent of patients[1]. The haematocrit of blood-stained ascites has been reported as 25–40 per cent[3,20].

4 Ultrasonography is valuable in the diagnosis of ruptured HCC because it is simple, quick and non-invasive. The rupture site appears as a hyperechoic area located around the tumour in 66 per cent of cases[21].

5 Computed tomography (CT) is also valuable because it is non-invasive and has a high power of resolution. CT can demonstrate a peripheral hepatic tumour and show

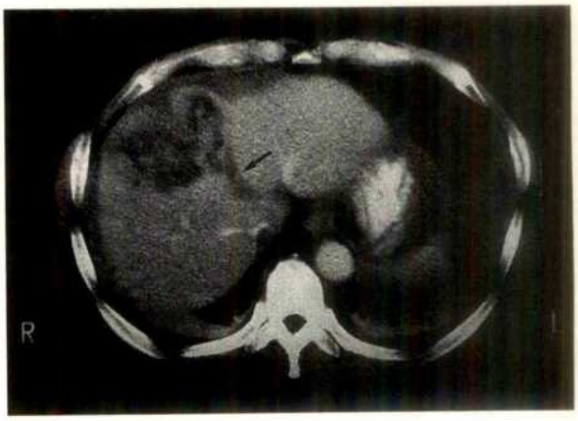

Fig. 4 Computed tomogram showing hepatocellular carcinoma located in the right anterior segment. Evidence of free fluid and absence of opacification of the middle hepatic vein (arrow) by intravenous contrast was found

Table 1 Results of treatment of ruptured hepatocellular carcinoma

Reference	Year	No. of cases	Resection	Plication	Hepatic artery ligation	Packing	TAE	Conservative treatment
Ong *et al.*[2]	1965	20	5 (5) (4) (1)	5 (5) (2) (0)	0	5 (5) (1) (0)	0	1 (–) (–) (–)
Balasegaram[12]	1968	10	3 (3) (2) (0)	3 (3) (3) (0)	0	1 (1) (0) (0)	0	2 (0) (0) (0)
Ong and Taw[25]	1972	42	13 (12) (7) (2)	1 (–) (–) (–)	12 (12) (5) (0)	8 (5) (2) (0)	0	5 (–) (0) (0)
Mokka *et al.*[17]	1976	5	2 (2) (2) (1)	2 (2) (2) (0)	1 (1) (1) (0)	0	0	0
Nagasue and Inokuchi[6]	1979	11	4 (4) (3) (1)	1 (1) (0) (0)	3 (2) (1) (0)	1 (1) (0) (0)	0	1 (–) (0) (0)
Chearanai *et al.*[3]	1983	63	1 (1) (1) (0)	3 (–) (–) (–)	26 (24) (–) (–)	6 (–) (–) (–)	0	26 (7) (4) (0)
Nouchi *et al.*[26]	1984	4	0	0	0	0	4 (3) (3) (2)	0
Sato *et al.*[20]	1985	6	0	0	0	0	6 (6) (5) (0)	0
Chen *et al.*[16]	1986	3	3* (–) (3) (–)	0	0	0	3 (3) (3) (–)	0
Hirai *et al.*[19]	1986	47	0	0	0	0	14 (14) (–) (0)	33 (–) (0) (0)
Hsieh *et al.*[23]	1987	17	0	0	0	0	17 (17) (12) (2)	0
Lai *et al.*[4]	1989	60	7 (5) (4) (–)	2 (2) (1) (1)	47 (32) (11) (1)	0	0	4 (–) (–) (–)
Dewar *et al.*[14]	1991	38	11 (4) (5) (0)	8 (–) (2) (0)	12 (–) (3) (0)	0	4 (4) (–) (0)	2 (–) (–) (0)
Miyamoto *et al.*[1]	1991	172	31 (–) (23) (13) 21* (–) (21) (15)	30 (–) (11) (2)	10 (–) (4) (0)	0	57 (–) (40) (17)	14 (–) (4) (0)
Okazaki *et al.*[24]	1991	38	0	0	0	0	38 (38) (24) (2)	0
Cherqui *et al.*[27]	1993	5	4 (4) (3) (1)	0	1 (0) (0) (0)	0	0	0
Corr *et al.*[21]	1993	14	1 (–) (–) (–)	0	0	0	9 (8) (6) (–)	4 (–) (–) (–)
Xu and Yan[18]	1994	87	2 (–) (0) (0) 29* (–) (–) (5)	7 (–) (3) (–)	9 (–) (4) (–)	0	0	68 (–) (33)* (5)*
Total†		642	84 (40 of 50 (80)) (54 of 83 (65)) (19 of 76 (25)) 53* (–) (24 of 24 (100)) (20 of 50 (40))	62 (13 of 13 (100)) (24 of 58 (41)) (3 of 51 (6))	121 (71 of 90 (79)) (29 of 95 (31)) (1 of 86 (1))	21 (12 of 15 (80)) (3 of 15 (20)) (0 of 15 (0))	152 (93 of 95 (98)) (93 of 134 (69)) (23 of 140 (16))	160 (7 of 28 (25)) (8 of 81 (10)) (0 of 83 (0))

TAE, transcatheter arterial embolization. The first set of parentheses in each column indicates the number of patients with bleeding successfully controlled, the second set indicates the number surviving at 1 month, and the third set indicates the number surviving at 1 year. *Patients with second-stage hepatectomy. †Values in parentheses are percentages derived from reports with sufficient information

free intraperitoneal fluid with areas of high attenuation close to the tumour, representing acute blood clotting, in almost every case[22]. The scan may demonstrate an unopacified hepatic vein, indicating that the draining vein is obstructed (*Fig. 4*).

6 Angiography is useful. The site of rupture is demonstrated by extravasation of radiographic contrast agent in 20–36 per cent of cases[19,23]. Angiography can also demonstrate tumour invasion of the portal vein in 36–45 per cent of patients[20,24].

An early diagnosis should be made to avoid delay in treatment. Clinical awareness and prompt non-invasive radiological investigations are the keys to such early diagnosis. Ruptured HCC should be suspected in any patient with a known history of cirrhosis or carcinoma presenting with acute epigastric pain. It should also be suspected in men of Asian or African origin suffering from sudden abdominal pain or haemoperitoneum.

Treatment

Ruptured HCC causes severe bleeding, hypotension and hypoperfusion of the liver. As it occurs mainly in those with cirrhosis, many patients lapse into liver failure secondary to hepatocyte necrosis[1]. It is, therefore, necessary to stop the bleeding and restore the blood pressure, and preferably to remove the HCC, as early as possible. One-stage hepatectomy may seem to be ideal for these purposes if it can be accomplished quickly, especially if the tumour is peripherally located or is pedunculated. However, in a patient who requires formal lobectomy, the length of time required, blood loss induced and resection of adjoining functioning liver parenchyma may actually accentuate the problem of liver failure. As hepatectomy is often performed in hurried and unfavourable conditions, and the patient may have a pre-existing coagulopathy, postoperative bleeding occurs in 23–36 per cent of cases[14,25]. Hence, although patients may not succumb to liver failure immediately and the 30-day survival rate is reported to be about 65 per cent (*Table 1*), many patients may not be discharged from hospital and die eventually from liver failure. Thus Lai *et al.*[4] reported that the hospital mortality rate for one-stage anatomical lobectomy was 75 per cent. In addition, as the operation is performed without the advantage of detailed investigation to delineate the extent of tumour within the liver, the resection margin is often positive for HCC; intrahepatic recurrence is high after hepatectomy[14]. To sum up the available literature, the 1-year survival rate is normally only 25 per cent (*Table 1*), but an exception is the report by Miyamoto *et al.*[1]. They described a 1-year survival rate of 42 per cent, but without mentioning the type of patients chosen for one-stage hepatectomy and the extent of resection. Their good outcome may be the result of selection of low-risk patients. Nevertheless, their report suggests that one-stage resection is feasible, especially when an experienced surgeon is available, the tumour is easily excised, and intraoperative ultrasonography is used to assess the extent of the tumour and to guide the line of parenchymal transection.

To avoid prolonged duration of anaesthesia during the acute episode, haemostasis followed by relaparotomy and hepatectomy is the alternative to one-stage resection. Such a two-stage method has the advantage of allowing the patient to recover from haemorrhagic shock and liver dysfunction, and a detailed evaluation to be made of the extent of tumour spread and functional liver reserve. The reported results of this approach are good; the 1-year survival rate is about 40 per cent[1,18]. However, such good results are artificial because, invariably, only patients with good liver function and with locally confined tumour are chosen for relaparotomy. Some investigators argue that one-stage resection is preferable to the two-stage technique because the latter approach allows cancer cells to disperse into the peritoneal cavity and grow[12,25]. This argument may not be valid because it is doubtful that one-stage hepatectomy, even with peritoneal lavage, can be effective in eradicating cancer cells that have already dispersed into the peritoneal cavity at the time of rupture.

The haemostatic methods which may be directed at the site of rupture include suture plication, packing, argon beam coagulation, microwave coagulation or injection of absolute alcohol into the tumour. Suture plication is usually impossible because the tumour is friable[12] and there is a risk of the needle going through the tumour with subsequent tumour dissemination. Suture plication is also unlikely to be applicable to bleeding points that are multiple or located at an inaccessible site. Packing is feasible for a tumour located under the diaphragm, because the diaphragm exerts a tamponade effect. It is also applicable for situations where the bleeding is in the form of oozing rather than active haemorrhage[23], but it is less useful for HCC located on the inferior surface of liver. Overall, packing is effective in controlling bleeding in about 80 per cent of cases (*Table 1*), but carries the risk of rebleeding after the removal of packs within 24–48 h after surgery. It also carries a risk of infection and so predetermines the date of relaparotomy for pack removal. Nevertheless, packing allows transfer of the patient to a major hospital where expert care is available. Argon beam coagulation is an effective method of controlling bleeding from the cut liver surface during hepatectomy. It should be equally effective in the case of ruptured HCC if the bleeding is not profuse, but application of the argon beam for ruptured HCC has not been described in the literature. Use of microwaves[28] and absolute alcohol[29] have been reported and seem to be effective in coagulating the tumour and so controlling bleeding, but large-scale experience of such methods is not available.

Since HCC is mainly supplied by the hepatic artery while the rest of the functioning liver parenchyma is dependent on portal vein blood supply, hepatic artery ligation is a logical and popular treatment, provided the portal vein is patent and the portosuprahepatic blood flow is normal[3,30]. In HCC with arterioportal venous shunting, hepatic artery ligation has the added advantage of reducing the degree of portal hypertension[3]. It is effective in controlling 68–92 per cent of bleeding HCCs[3,4], but the hospital mortality rate is high (54–77 per cent)[3,4]. There are many reasons for inefficiency in achieving haemostasis in some cases. Plengvanit *et al.*[31] thought that this was due to the rapid development of collateral vascularization through minor arteries. It may be the incorrect artery that is hurriedly ligated or the bleeding may be from a parasitic artery or vein. Persistent bleeding is definitely a disastrous situation which contributes to the high hospital mortality rate of ruptured HCC, but hepatic artery ligation itself may also be responsible. This is because the cirrhotic liver, in contrast to the normal liver, derives 50 per cent of blood supply from the hepatic artery. Ligation of the artery, therefore, may be detrimental to the cirrhotic liver. In addition, the procedure of hepatic artery ligation makes subsequent TAE difficult or impossible[24]. To reduce the extent of ischaemic damage to the liver and to allow TAE for treatment of later development of HCC in the contralateral lobe, selective ligation of the branch of the artery supplying the liver lobe bearing the tumour is the logical approach. However, this method did not reduce the hospital mortality rate in eight patients so treated[4]. In general, laparotomy and general anaesthesia remove the tamponade effect of haemoperitoneum and accentuate the problems of further bleeding, shock and hypoxic damage to the liver; laparotomy is undesirable in patients with poor liver function.

To avoid general anaesthesia and to stop the bleeding without operation, TAE or transcatheter arterial chemoembolization has been used[16,19–21,23,24,26]. These two methods have the advantage over hepatic artery ligation in that the angiographic catheter can be advanced selectively into the branch supplying the tumour and so damage to uninvolved liver tissue is much reduced; theoretically collateral development should be less pronounced than after hepatic artery ligation[24]. Even though Okazaki *et al.*[24] reported that there was no significant difference in prognosis between patients who underwent selective or non-selective TAE, the selective approach is logical, especially for cirrhotic liver with poor function. Hepatic angiography identifies alternative arteries which may supply the tumour and the correct artery can be occluded, instead of blind obliteration as in the case of hepatic artery ligation. This approach allows stabilization of the patient and planning for laparotomy, if the HCC is resectable. If the tumour is irresectable and if Gelfoam (Ferrosan, Denmark) is used in the embolization, the catheter procedure can be repeated every 3–4 months as recanalization of the hepatic artery may occur[32]. The use of stainless steel coils for permanent occlusion of the hepatic artery causes subsequent procedures to be difficult and is not advisable[20,24]. Lipiodol (Laboratoire Guerbet, France) mixed with chemotherapeutic agent is often infused before embolization of the artery, and absolute alcohol mixed with lipiodol has also been employed successfully in this situation[33]. Using TAE, haemostasis is achieved successfully in 75–100 per cent of patients, but recurrent bleeding and hepatic failure may occur[24,26]. If TAE is the sole procedure for treatment of ruptured HCC, the 1-month survival rate is about 69 per cent (*Table 1*). However, TAE has the limitation that an experienced interventional radiologist is urgently required and it is not applicable when the main trunk of the portal vein is totally obstructed[21]. Although Okazaki *et al.*[24] did not consider portal vein tumour thrombus as a contraindication to TAE, and demonstrated that the results of TAE were no different in patients with or without portal vein tumour thrombus, details were not given about the completeness of portal vein occlusion in their patients. It has generally been agreed that partial occlusion of the portal vein should not be considered as an absolute contraindication to TAE, and satisfactory long-term outcome in non-ruptured HCC has been reported.

Conservative treatment has been adopted by many surgeons when the patient is moribund or as a 'wait-and-see' policy for those who are judged unlikely to tolerate an invasive procedure[18]. The reported results of conservative treatment are, therefore, generally poor; the hospital mortality rate is 85–100 per cent[3,19] and the median survival is only 13 days[19]. However, some patients are haemodynamically stable on presentation or after resuscitation. For them, it is doubtful whether any urgent and invasive procedure is necessary. Conservative treatment was adopted as the first treatment in one study and the immediate results were not inferior to those of emergency surgery[18]. Irrespective of policy, conservative treatment that consists of blood replacement, correction of coagulopathy and cardiovascular monitoring should be part of an active treatment process that prepares patients for operative or non-operative intervention.

The criteria of selection for patients for different procedures have not been rigidly formulated in previous reports. Selection probably depends on the condition of the patient, belief of surgeon, availability of an interventional radiologist and whether or not laparotomy has been undertaken. Comparison of results of different treatments is, therefore, difficult. Summing up all the reports, it appears that early success in haemostasis is best achieved by TAE or hepatic artery ligation. However, many more patients treated by hepatic artery ligation die within the first month from hepatic failure; the majority of patients treated by TAE die within the first year from tumour progression (*Table 1*). On the other hand, patients with early disease and good liver function who were chosen for one- or two-stage hepatectomy survived longer, even though the early mortality rate was high. Selection of patients for different procedures is necessarily individualized. The rational treatment appears to be TAE for initial haemostasis followed by hepatectomy if the carcinoma is resectable. However, it should be noted that some patients may be admitted to hospital in a moribund state and succumb rapidly before operative or non-operative intervention can be carried out. There are also situations in which patients are not treated energetically because ruptured HCC is considered a terminal manifestation of advanced disease. Few reports[3,4] mention this group of patients and the success of each procedure is often expressed as the percentage of patients treated and not as the percentage of all patients admitted with the complication. In future, reports on the subject of ruptured HCC should include patients who are not treated by any kind of intervention so that a complete picture may be obtained.

Prognosis

The prognosis of ruptured HCC is poor because many patients harbour advanced disease at presentation; the incidence of concomitant cirrhosis is high, the diagnosis may be delayed and malignant cells may have been dispersed into the peritoneal cavity. Shock at presentation[14], hyperbilirubinaemia[24] and advanced cirrhosis[4] are poor prognostic factors, irrespective of treatment modality. Nevertheless, occasional long-term survival is possible after hepatectomy[27]. Maximum effort should, therefore, be given to potentially salvageable cases. Compared with non-rupture, the long-term survival rate of patients with ruptured HCC is generally worse, but no statistical comparison has been made. To allow a full evaluation of prognosis, comparison between ruptured and non-ruptured cases with respect to tumour node metastasis staging of the disease and the severity of liver functional impairment would be valuable.

Conclusion

Apart from a few cases of prolonged survival after hepatectomy, the overall prognosis of patients with spontaneous rupture of HCC is poor. The hypothesis that it is occlusion of the vascular outflow of HCC which leads to rupture is attractive, but this needs further research. Based on such a hypothesis, interruption of the hepatic artery, either by hepatic artery ligation or TAE, is the logical approach, but studies must be done to explain why it is not effective in some cases. Improvement of the overall outcome will depend on early diagnosis, prompt supportive treatment, early non-operative intervention and aggressive surgery for resectable cases once liver function improves.

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British Journal of Surgery 1996, 83, 608–619

Review

Nutritional pharmacology and malignant disease: a therapeutic modality in patients with cancer

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It is now established that certain nutrients have a significant effect on cellular metabolism and growth, tissue repair and regeneration, and modulation of host defences. So far, however, potential clinical benefits have been difficult to demonstrate. Nevertheless, the use of nutrients in combinations seems to have promise and may be associated with a reduction in infectious complications and length of hospital stay. Nutritional pharmacology in the future may be able to improve tumour response to chemotherapy and may minimize the metabolic effect of cachexia.

A balanced diet is necessary for maintenance of normal body functions and good health. Recently, it has been recognized that certain nutrients can also have marked biological effects on cells and tissues, both normal and abnormal. Some nutrients can also regulate aspects of the inflammatory and immune responses if given in pharmacological amounts (in excess of normal daily requirements). In malignant disease, metabolic disturbances are common and host defences are frequently compromised, particularly in patients with advanced disease. This review focuses on a selected group of nutrients (L-arginine, L-glutamine, essential fatty acids (EFAs) and polyribonucleotides) that have been shown to modulate inflammation and immune reactivity. Their normal physiological roles, their effects when given in pharmacological doses and their potential application in the treatment of patients with malignant disease are discussed.

L-Arginine

L-Arginine is an amino acid which is essential for growth in many young animals but does not appear to be essential in humans, either in children or adults[1,2]. In conditions such as stress, sepsis and trauma, it may become semi-essential[3]. Under these circumstances there is a reduction in plasma L-arginine concentration and inadequate endogenous synthesis of L-arginine[3]. The average Western daily diet contains approximately 5 g L-arginine (red meat, fish, poultry, cereals and dairy produce). The kidneys also take up circulating citrulline (a product of glutamine metabolism in the gut) and metabolize it to L-arginine[4]. Further synthesis occurs in the liver through the urea cycle. The physiological role of L-arginine is as a substrate for protein, creatinine and polyamine synthesis[5–7]. It is also a substrate for production of nitric oxide via the deiminase pathway[8,9]. Nitric oxide may exert its effects by activating guanylate cyclase in cells, which influences a variety of cellular processes[9]. There are three aspects of malignant disease in which L-arginine has been investigated: (1) effects on nitrogen metabolism and wound healing; (2) stimulation of host antitumour defences; and (3) effects on tumour cell metabolism.

Nitrogen metabolism

Following injury there is an increased requirement for L-arginine to maintain optimal metabolic function. Animal studies have shown that supplementation with L-arginine results in an increase in nitrogen retention and body-weight following surgical trauma[10,11]. Subsequent studies, in patients undergoing cholecystectomy, have demonstrated that L-arginine supplementation of 15 g/day for 3 days significantly reduces nitrogen excretion, compared with that in patients receiving an isonitrogenous regimen[12]. In patients with gastrointestinal malignancy, L-arginine supplementation of 25 g/day for 7 days is associated with an improvement in nitrogen balance at 5–7 days after surgery[13]. These studies are summarized in *Table 1*.

Wound healing

L-Arginine has beneficial effects on wound healing. Studies in animals have shown that L-arginine supplementation increases wound breaking strength, compared with that in animals receiving a diet deficient in this amino acid[17]. Other studies have shown that animals receiving L-arginine exhibit enhanced wound healing and collagen deposition[18]. The mechanisms of these actions are unclear but may be related to increased secretion of growth hormone (an intact hypothalamopituitary axis is necessary for L-arginine to exert its effect[19]), activation of *in situ* macrophages in wounds or alterations in the nitric oxide pathway, and changes in vascular permeability[3]. Alternatively, L-arginine is a precursor for proline and hydroxyproline and, thus, collagen synthesis[20].

The effect of L-arginine on wound healing in humans, as assessed by modulation of collagen synthesis, has also been evaluated. Barbul *et al.*[14] implanted polytetrafluoroethylene tubing into the subcutaneous tissue of volunteers. After 2 weeks of supplementation with L-arginine 25 g/day, the amount of hydroxyproline in the

Paper accepted 22 November 1995

Table 1 Effect of L-arginine supplementation on metabolism

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Elsair *et al.*[12]	1978	Gallbladder disease	18	Patients received TPN with or without L-arginine 15 g/day for 3 days after cholecystectomy	L-Arginine supplementation resulted in a 60 per cent reduction in nitrogen excretion
Daly *et al.*[13]	1988	Gastrointestinal malignancy	30	Randomized to receive enteral nutrition with either L-arginine 25 g/day or glycine 43 g/day for 7 days after surgery	Mean daily nitrogen balance was the same in both groups but a positive nitrogen balance occurred only in the group receiving supplementary L-arginine between days 5 and 7. No difference in clinical outcome
Barbul *et al.*[14]	1990	Healthy volunteers	36	Standard diet and randomized to receive either L-arginine 25 or 17 g/day, or no supplementation	L-Arginine-supplemented groups had significantly increased collagen synthesis (25 g greater than 17 g L-arginine per day)
Park *et al.*[15]	1992	Breast cancer	20	Patients randomized to either a standard diet or standard diet and L-arginine 30 g/day for 3 days	Fractional rate of protein synthesis in the tumour *in vivo* was increased in the L-arginine-supplemented patients by approximately 150 per cent, compared with that in non-supplemented patients
Brittenden *et al.*[16]	1994	Breast cancer	44	Patients received standard diet and L-arginine 30 g/day for 3 days before primary chemotherapy on six occasions	Response rate of the primary tumour to chemotherapy was enhanced by L-arginine supplementation compared with historical controls (92 *versus* 72 per cent). Effect on disease recurrence or survival not known

TPN, total parenteral nutrition

tubing (a measure of collagen synthesis) was determined. The tubing in volunteers supplemented with the amino acid had more than double the content of hydroxyproline compared with that in those not receiving L-arginine[14].

Effects on host defences

Studies in experimental animals have revealed that dietary supplementation with L-arginine increases thymic weight[18,21] and reduces thymic involution after trauma[18]. Also, in both healthy and traumatized animals, L-arginine supplementation enhances splenocyte and thymocyte responses to polyclonal mitogens[22]. Studies in humans demonstrate that if lymphocytes taken from healthy volunteers are incubated *in vitro* with L-arginine the response to mitogens is substantially increased[23]. These workers evaluated the effects of dietary supplementation with L-arginine 30 g/day for 7 days on the immune system. Although there were no changes in the total lymphocyte count or ratio of T and B lymphocytes, there was an increased response of peripheral blood lymphocytes to mitogen[14]. Studies in volunteers have confirmed that 7 days of dietary supplementation with L-arginine 25 g/day results in an enhanced response of peripheral blood lymphocytes when stimulated *in vitro* with mitogens[14]. The effect of L-arginine supplementation in the postoperative period has been investigated by Daly *et al.*[13]. Some 30 patients with gastrointestinal cancer were randomized to receive either L-arginine 25 g/day or isonitrogenous glycine 43 g/day for 7 days after surgery as part of an enteral diet. L-Arginine supplementation resulted in an enhanced response of peripheral blood lymphocytes to mitogens on the seventh day after operation compared with the first day, and was also associated with an increased number of circulating CD4-positive T cells. There were, however, no differences in complications between the two groups.

Natural cytotoxicity, mediated by natural killer (NK) and lymphokine-activated killer (LAK) cells, is thought to play an important role in the prevention of dissemination of malignancy and in the destruction of established tumour deposits[24]. Animal studies have shown that L-arginine supplementation results in an enhanced NK and LAK cell cytotoxicity when these cells are stimulated with interferon (IFN) γ, polyinosinic–polycytidylic acid or interleukin (IL) 2[25,26]. Park *et al.*[27] demonstrated that *in vitro* supplementation with L-arginine of peripheral blood lymphocytes results in an enhancement of NK and LAK cell cytotoxicities. Furthermore, if volunteers have their diet supplemented with L-arginine 30 g/day for 3 days, there are significant increases in blood NK and LAK cell activities[27]. A similar effect has been demonstrated in patients with breast cancer and other studies have shown that L-arginine repeatedly enhances NK cell activity following sequential cycles of chemotherapy[28,29]. These findings are summarized in *Table 2*.

The studies discussed above addressed the effects of L-arginine on circulating immune cells. More recently, other investigators have evaluated the effect of L-arginine on the tumour microenvironment. Patients with colorectal cancer were randomized to receive either a standard diet or a standard diet supplemented with L-arginine 30 g/day for 3 days before surgery[30]. At the time of surgery, tumour biopsies were taken and the composition of the infiltrating lymphoreticular cells analysed. L-Arginine supplementation resulted in an increased number of CD16-positive and CD56-positive cells (NK and LAK cells respectively) in the tumour microenvironment, compared with that in tumours from patients not receiving supplementary L-arginine. L-Arginine has been shown to

Table 2 Effect of L-arginine supplementation on host defences

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Daly et al.[13]	1988	Gastrointestinal malignancy	30	Patients received enteral nutrition and were randomized to either L-arginine 25 g/day or glycine 43 g/day for 7 days after surgery	Increased *in vitro* response of lymphocytes to mitogens on the first postoperative day and increased number of CD4-positive lymphocytes. No difference in clinical outcome or infectious complications
Barbul *et al.*[14]	1990	Healthy volunteers	36	Standard diet and randomized to receive either L-arginine 25 or 17 g/day, or no supplementation	Increased *in vitro* response of lymhocytes to mitogens with L-arginine supplementation after 7 days
Barbul *et al.*[23]	1981	Healthy volunteers	27	Some 21 volunteers received L-arginine 30 g/day for 7 days; six volunteers received L-arginine 30 g/day for 3 days	L-Arginine supplementation resulted in enhanced *in vitro* responsiveness of peripheral blood lymphocytes to mitogens; effects present after 3 days but more marked by day 7
Park *et al.*[27]	1991	Healthy volunteers	13	Standard diet supplemented with L-arginine 30 g/day for 3 days	NK and LAK cell cytotoxicity increased by 91 and 58 per cent respectively; circulating CD56-positive (LAK) cell numbers increased following L-arginine supplementation
Brittenden *et al.*[28]	1994	Locally advanced breast cancer	24	Standard diet supplemented with L-arginine 30 g/day for 3 days	Lymphocyte responses to mitogens, NK and LAK cell cytotoxic activities all increased but no change in CD16-positive (NK) or CD56-positive (LAK) cell numbers after L-arginine supplementation
Brittenden *et al.*[29]	1994	Locally advanced breast cancer	16	Standard diet supplemented with L-arginine 30 g/day before chemotherapy on six occasions	Stimulation of NK and LAK cell cytotoxicity by L-arginine supplementation on each of the six occasions
Bruce *et al.*[30]	1995	Colonic cancer	18	Randomized to standard diet or standard diet supplemented with L-arginine 30 g/day for 3 days	Histological examination of the tumour microenvironment showed that the L-arginine-supplemented group had increased infiltration by CD16-positive (NK), CD56-positive (LAK) cells. No changes in CD2-positive, CD3-positive cells within the tumours

NK, natural killer; LAK, lymphokine-activated killer

activate macrophage antitumour cytotoxic effector mechanisms[31–33]. The exact method by which it mediates these effects is not known, but it may include increased production of hormones, polyamines, cytokines and nitric oxide[34]. However, the effects of supplementation with L-arginine on macrophage function in humans *in vivo* still require evaluation.

Effects on tumour growth

The effect of L-arginine on tumour growth has been investigated over the past 50 years with conflicting results. *In vitro*, it can both inhibit (breast)[35] and stimulate (lung)[36] cancer cells. *In vivo* animal studies have also demonstrated both stimulation[37,38] and inhibition[39,40] of tumour growth. It has been suggested that if a tumour is weakly immunogenic then L-arginine supplementation may stimulate tumour growth, there being a lack of appropriate recognition and suitable anticancer response by the immune system. Conversely, if the tumour is strongly immunogenic then the effects of L-arginine on host antitumour defence mechanisms may predominate, resulting in an inhibition of tumour growth[41]. The effect of L-arginine on tumour growth in humans *in vitro* had not been studied until recently. In 1992, Park *et al.*[15] described the effect of dietary L-arginine on tumour growth in patients with breast cancer. Patients were randomized to receive either a standard diet or the same diet supplemented with L-arginine 30 g/day for 3 days. With L-arginine supplementation the *in vivo* rate of tumour protein synthesis (previously shown to correlate with cell growth) was more than doubled, and there was increased expression of the nuclear activation antigen, Ki67, by the malignant cells[15]. This suggests that L-arginine induces a stimulation of tumour cell metabolism and proliferation. Previous studies demonstrated that the sensitivity of a tumour to chemotherapy depends on the number of cells in the S phase of the cell cycle[42]. Thus activation of tumour cell metabolism should increase the likelihood of a response to chemotherapeutic agents. The feasibility of such an approach has recently been reported in humans[16]. Patients with breast cancer were treated with neoadjuvant chemotherapy, given on six occasions at intervals of 21 days. For 3 days before the administration of chemotherapy, the diet of these patients was supplemented with L-arginine 30 g/day. The response rate of the primary tumours, according to Union Internacional Contra la Cancrum criteria, exceeded 90 per cent. By comparison, the response rate in historical control patients, treated with an identical chemotherapeutic regimen but without L-arginine, was 72 per cent[43]. However, further careful randomized studies are necessary to confirm these promising preliminary findings and to evaluate more fully the role of nutritional supplementation with chemotherapy.

L-Glutamine

L-Glutamine is synthesized *de novo* in skeletal muscle by transamination of other amino acids by the enzyme glutamine synthetase[44]. It is the most abundant amino acid in the body, comprising approximately 50–60 per cent of the intracellular free amino acid pool[45], and has the highest plasma concentration of all amino acids. L-Glutamine is considered to be a non-essential amino acid and under normal physiological circumstances it has several important roles. First, it acts as a nitrogen shuttle between certain tissues and is a precursor for synthesis of purines, pyrimidines and amino acids; it is essential for normal cellular proliferation and tissue growth[46]. Second, a direct relationship exists between the rate of skeletal muscle protein synthesis and the intracellular L-glutamine concentration[47]. Third, it is an important fuel for enterocytes, colonocytes[48], kidney[49], lymphocytes[50] and fibroblasts[51]. In pathological states, such as trauma, prolonged sepsis and major burns, there is an increased efflux of amino acids, including L-glutamine, from skeletal muscle[52,53], with a resultant fall in intracellular L-glutamine levels[54]. Although the plasma concentration may be maintained initially, a continuing demand results in a fall in plasma levels[55]. The magnitude of the fall in free intracellular L-glutamine concentration in patients with sepsis correlates with survival[56]. Therefore, attempts have been made to correct these disturbances by L-glutamine supplementation.

Nitrogen metabolism

The effect of supplementing parenteral nutrition with L-glutamine or a glutamine source (e.g. ornithine-α-glutarate) on nitrogen balance and skeletal muscle protein synthesis has been evaluated in patients undergoing cholecystectomy[57,58]. Patients received either standard parenteral nutrition or an isonitrogenous L-glutamine-supplemented regimen for 3 days after operation. L-Glutamine supplementation resulted in a decrease in the fall in skeletal muscle free L-glutamine concentration and a substantial reduction in whole body nitrogen loss. However, there was no change in skeletal muscle protein synthesis compared with the control group.

Another study[59] evaluated 12 patients with colorectal cancer, randomized to receive either a parenteral regimen (230 mg nitrogen per kg and 166 kJ/kg daily) containing either L-alanyl-L-glutamine (54 mg peptide nitrogen per kg per day) or an isonitrogenous amount of alanine and glycine[59]. This was given intravenously for the first 5 days after operation. There was a significant reduction in the daily negative nitrogen balance and an increase in the level of L-glutamine in skeletal muscle in patients receiving supplementary L-glutamine. However, this study was too small to evaluate whether these changes had any effect on clinical outcome.

An important study by Ziegler and colleagues[60] examined whether L-glutamine supplementation has an effect on clinical outcome. Forty-five patients undergoing bone marrow transplantation for haematological malignancy were enrolled. Parenteral nutrition, containing the estimated protein and calorie requirements, was commenced on the first day after transplantation. Half of the patients had L-glutamine supplementation 0·57 g per kg body-weight per day for approximately 28 days; this represents approximately seven times the normal daily intake of L-glutamine. Patients receiving L-glutamine supplementation had improved nitrogen balance, fewer infections and a shorter hospital stay than those not receiving it (*Table 3*).

Effects on tumour growth

Certain tumour cells and tumour cell lines are dependent on L-glutamine for maintenance of growth and proliferation[62–64]. The glutamine antimetabolite, acivicin, can inhibit tumour growth, both *in vitro* and *in vivo*[65,66]. Attempts have been made to stimulate muscle mass in tumour-bearing animals receiving parenteral nutrition, but

Table 3 Effect of glutamine supplementation on metabolism and host defences

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Hammarqvist *et al.*[58]	1989	Cholecystectomy	22	TPN or TPN supplemented with glutamine	Glutamine supplementation reduced loss of intracellular glutamine in muscle and reduced nitrogen loss, but did not change muscle protein synthesis
Stehle *et al.*[59]	1989	Colorectal cancer	12	TPN or L-alanyl-L-glutamine-supplemented TPN for 5 days after operation	Improved nitrogen balance in patients receiving L-alanyl-L-glutamine supplementation
Ziegler *et al.*[60]	1992	Haematological malignancy	45	TPN or TPN supplemented with glutamine for approximately 28 days after bone marrow transplantation	Improved nitrogen balance, reduced incidence of infection and reduced hospital stay in patients receiving glutamine supplementation
O'Riordain *et al.*[61]	1994	Colorectal cancer	20	TPN or glutamine-supplemented TPN for days 1–6 after operation	Increased T cell DNA synthesis; no difference in IL-2, IL-6 or TNF production by peripheral blood mononuclear cells; no difference in clinical outcome

TPN, total parenteral nutrition; IL, interleukin; TNF, tumour necrosis factor without stimulating tumour growth, by giving an anabolic agent (clenbuterol) in combination with a glutamine antagonist (acivicin)[67]. Results have been encouraging; animals receiving clenbuterol and acivicin have an increased skeletal muscle mass and gut mass, and inhibition of tumour growth, compared with animals receiving parenteral nutrition alone.

Effects on host defences

L-Glutamine is necessary for lymphocyte and macrophage function. Animal studies have shown that L-glutamine supplementation *in vitro* enhances various aspects of lymphocyte function[50]. The effects of L-glutamine supplementation on lymphocyte function in humans have not been well documented. Recently, O'Riordain and colleagues[61] investigated the effects of L-glutamine supplementation in 20 patients, 18 of whom had colorectal cancer. Patients were randomized to receive either conventional parenteral nutrition 0·2 g nitrogen per kg per day or an isocaloric, isonitrogenous regimen containing 0·18 g L-glutamine per kg per day, from days 1 to 6 after operation. L-Glutamine supplementation resulted in a significant increase in T cell lymphocyte DNA synthesis, but it did not alter production of IL-2, IL-6 or tumour necrosis factor (TNF) by peripheral blood mononuclear cells. There was no difference in infection rate between the two groups of patients (*Table 3*). However, while supplementation with amino acids can have beneficial effects, there are potential problems with diets imbalanced in their amino acid composition. For example, they may lead to serum imbalances of amino acids and to metabolic complications, such as hyperammoniaemia and acidosis.

Essential fatty acids

Certain fatty acids cannot be synthesized by mammals and are required in the diet for maintenance of health. These EFAs, which are polyunsaturated, play key roles in the metabolism of both normal and malignant cells. They are composed of two main types: the n-6 series, derived from linoleic acid (e.g. γ-linolenic acid (GLA) and arachidonic acid (AA)), and the n-3 series, derived from α-linolenic acid (e.g. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). The usual dietary intake of the n-6 EFAs is approximately 200–780 mg/day, and for EPA–DHA it is approximately 250 mg/day (dependent on fish consumption).

The main physiological functions of the EFAs are concerned with the structure and function of cell membranes[68], and in the synthesis of intermediate compounds that regulate cellular metabolism[69]. They control the biomechanical properties of cell membranes, and so can alter the expression and function of membrane-bound receptors[70,71]. The regulatory intermediates formed from EFAs include prostaglandins, leucotrienes and hydroxy acids, collectively termed eicosanoids and derived predominantly from AA and EPA[69]. These eicosanoids have many functions including regulation of intracellular calcium and second messenger molecules, and modulation of inflammation and host defences[72–75].

Effects on host defences

Studies in animals have demonstrated that after injury there is an increase in the production of prostaglandin (PG) E_2 by macrophages[76] and an increase in circulating levels of PGE_2[77]. Dietary supplementation with n-3 fatty acids results in the production of the 3 series rather than the 2 series of prostaglandins. The PG_3 compounds are less immunosuppressive than PG_2 products[78]. This may be beneficial because PGE_2 suppresses lymphocyte function and NK cell activity, and reduces IL-1 production by macrophages[79–81].

However, incubating human peripheral blood lymphocytes of healthy volunteers *in vitro* with EFAs (e.g. EPA, DHA, AA) significantly reduces the lymphoproliferative response to various polyclonal mitogens and inhibits the production of IL-2[82]. The effect of EFA supplementation *in vivo* has been studied. Meydani *et al.*[83] supplemented the diets of healthy women with EPA 1680 mg/day, DHA 720 mg/day and other fatty acids 600 mg/day for 3 months. At the end of this period there was a reduction in the serum level of IL-1β, IL-2 and IL-6, and inhibition of the *in vitro* T cell response to mitogens. These effects were more marked in older than younger women.

The effects of prolonged dietary supplementation with high doses of EFAs on aspects of the immune system in patients with advanced colorectal cancer have also been investigated[84]. EFA supplementation (GLA 2336 mg/day, DHA 320 mg/day, EPA 2112 mg/day) for up to 6 months results in a significant inhibition in the reactivity of peripheral blood lymphocytes to mitogens *in vitro* and a reduction in the circulating numbers of CD4-positive (T helper) and CD8-positive (T suppressor/cytotoxic) cells. A reduction in the response to mitogens is observed within 15 days of EFA administration. Some 3 months after cessation of EFA supplementation the responsiveness to mitogens returns to pretreatment values. Prolonged administration of high doses of EFAs also results in inhibition in natural cytotoxicity, NK and LAK cell cytotoxicity[85], and the serum concentrations of IL-1, IL-2, IL-4, IL-6, TNF-α and IFN-γ are reduced[86] (*Table 4*). Significant changes may be seen after 3 months of EFA ingestion, after which the levels of these cytokines steadily decline to minimum levels after 6 months of EFA intake. Three months after cessation of ingestion of the EFAs the cytokine levels return to presupplementation levels. These changes are not observed in patients with advanced colorectal cancer who are not receiving EFA supplementation. The mechanisms of these effects are unclear but EFA-induced alterations in cell membrane composition and fluidity[89], or alterations in the production of prostaglandins, may be important[90].

These effects on cytokines may seem detrimental to the immune response. However, recent studies have evaluated the role of cytokines in the aetiology of cancer cachexia. Evidence suggests that TNF-α, IL-6 and IL-1[91–93] may be important aetiological factors. In animal models of cachexia, dietary supplementation with EFAs improves nutritional status and reverses weight loss associated with cancer[94]. Studies are required to evaluate the possible beneficial effects of EFAs in patients with cancer who are losing weight.

Effects on tumour growth

Polyunsaturated fatty acids are susceptible to lipid peroxidation[95]. This process encompasses a series of reactions whereby certain reactive radicals, such as superoxide, hydroxyl radicals and oxygenated lipids, are produced. These products of lipid peroxidation, known to damage DNA, may have a physiological role in the

Table 4 Effect of dietary supplementation with essential fatty acids on host defences and antitumour status

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Meydani *et al.*[83]	1991	Volunteers	11	EPA 1680 mg/day and DHA 720 mg/day for 3 months to young women ($n = 5$) and older women ($n = 6$)	Reduced serum levels of IL-1β, IL-2 and T cell responses *in vitro* to mitogens. Effects greater in older women
Purasiri *et al.*[84]	1994	Colorectal cancer	30	Patients with advanced colorectal cancer were given GLA, EPA, DHA for 6 months	Reduction in peripheral blood lymphocyte responses *in vitro* to mitogens, and in CD4-positive (T helper) and CD8-positive (T suppressor) cell numbers after 15 days of EFA supplementation
Purasiri *et al.*[85]	1995	Colorectal cancer	20	As above	Reduction in NK and LAK cell cytotoxic activity of blood lymphocytes; reduction in numbers of CD16-positive (NK), CD56-positive (LAK) cells
Purasiri *et al.*[86]	1994	Colorectal cancer	30	Patients with localized colorectal cancer ($n = 10$) given GLA, EPA, DHA for 15 days; patients with advanced colorectal cancer ($n = 20$) given GLA, EPA, DHA for 6 months	Serum levels of IL-1β, IL-2, IL-4, IL-6, TNF-α, IFN-γ significantly reduced after 2 months of treatment
Van de Merwe *et al.*[87]	1987	Hepatocellular carcinoma	11	GLA 800–1600 mg/day and linoleic acid 7–14 g/day continuously	Clinical improvement in all patients; reduction in tumour size in most cases
Naidu *et al.*[88]	1992	Glioma	6	Intratumoral administration of GLA 1 mg/day for 10 days	Substantial reduction in tumour size in all patients detected by computed tomography

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; GLA, γ-linolenic acid; EFA, essential fatty acid; IL, interleukin; TNF, tumour necrosis factor; IFN, interferon; NK, natural killer; LAK, lymphokine-activated killer

control of cell division. For example, tissues that proliferate rapidly tend to have lower levels of lipid peroxidation than those which proliferate more slowly[96–98]. It is also recognized that malignant cells are relatively resistant to peroxidation[99,100] and that the more rapid the growth of the tumour, the lower the rate of lipid peroxidation[100].

Malignant cells have markedly enhanced levels of antioxidants (e.g. vitamin E and oleic acid) and lower levels of the 6-desaturated EFA metabolites (derived from GLA and AA) compared with the normal tissues of origin. The reason for this is unclear but it may be due to an absence of or deficiency in the 6-desaturase enzymes[101]. The resultant lowering in the production of the substrates for lipid peroxidation is believed to lead to a failure of regulation of cell division. It has also been shown that the 6-desaturated polyunsaturated fat content is lower in human cancers associated with metastases than in localized tumours[102]. Studies, therefore, have been carried out to determine whether the 6-desaturase enzyme complex can be bypassed by the provision of GLA, AA and other related EFAs. These studies show that the addition of GLA to a range of malignant cells *in vivo* results in cell death within 5–10 days; normal cells are unaffected[103–106]. In some animals bearing mammary tumours the addition of GLA to the diet inhibits tumour growth[101,107].

Pilot studies have been carried out to evaluate the role of dietary supplementation with EFAs in patients with hepatoma[87]. Improvement in clinical condition and limited regression of tumour growth were noted. More recent work has demonstrated that the intratumoral administration of GLA in patients with cerebral gliomas results in a substantial reduction in tumour size[88]. Only one controlled clinical trial evaluating the effect of EFAs in human cancer has been reported to date. McIllmurray and Turkie[108] found that GLA treatment has no effect on survival in patients with Dukes C colorectal cancer compared with those receiving placebo (*Table 4*). Further work is required on the effects of individual fatty acids on different cancer types, because some EFAs may actually stimulate colorectal cancer cell lines[109].

Another possible role for EFAs in the treatment of malignancy is in combination with cytotoxic drug therapy. *In vitro* studies have demonstrated that preincubation of tumour cells with EFAs increases the subsequent cytotoxic effect[110]. However, if malignant cells are incubated in the presence of EFAs and either doxorubicin or cisplatin, although both the EFAs and drugs are cytotoxic, the combined effects are only additive[111].

Polyribonucleotides

Thirty years ago it was demonstrated that the loss of antibody-producing function in irradiated animals could be restored by giving the animals nucleic acid-rich material[112]. Because of the difficulties in extracting the active components from this material, synthetic polyribonucleotides were developed[113]. A range of polyribonucleotides has been evaluated in animal models, e.g. polyadenylic–polyuridylic acid (PAPU), and appears to have immunomodulatory effects. The mode of action of PAPU is unclear, but it is believed to modulate intracellular regulatory enzymes either by augmenting membrane signals or by providing appropriate precursors for cyclic nucleoside monophosphates[114].

Effects on host defences

PAPU alters both cell-mediated and humoral aspects of the immune system, possibly through induction of cytokine production (e.g. IFN-γ[115]). Administration of

PAPU in various animal models increases the number and function of circulating T lymphocytes[116], enhances delayed-type hypersensitivity reactions[117], increases activity of T suppressor cells[118], enhances non-specific and specific T cell cytotoxicity and stimulates natural cytotoxicity[119]. In humans, PAPU stimulates aspects of macrophage function[120] and either augments or suppresses antibody production[121]. PAPU also induces the release of IL-1β, IL-2, IL-6, TNF-α and IFN-γ[120,122].

Youn and colleagues[123] studied the effects of PAPU in patients with stomach cancer who had undergone gastrectomy and who, 10–15 days later, were randomized to receive either chemotherapy (5-fluorouracil and doxorubicin) and PAPU, or chemotherapy and placebo. PAPU administration resulted in an increase in NK cell cytotoxicity, whereas NK cell activity in the placebo group was unchanged. Khan *et al.*[124] have also investigated the effects of PAPU on natural cytotoxicity in patients with breast cancer. Patients were randomized to receive either PAPU or placebo, commencing before surgery and given again at intervals for 14 days after mastectomy. Surgery resulted in suppression of NK cell activity in patients receiving placebo. However, PAPU treatment abolished this postoperative immune suppression. In addition, there was a significant fall in the number of circulating NK cells in the placebo group but no such reduction in the patients receiving PAPU[124]. Do these changes in immune activity benefit patients in terms of survival? Several studies have evaluated the effect of PAPU on survival in patients with cancer; these are discussed below and summarized in *Table 5*.

Breast cancer. Lacour *et al.*[125,126] examined the effect of PAPU in 300 patients with breast cancer, randomized to receive either PAPU 30 mg intravenously or placebo, commencing 8–15 days after surgery and given at intervals of 1 week for 6 weeks. PAPU prolonged the 5-year actuarial survival rate (82 *versus* 72 per cent for patients receiving PAPU and placebo respectively) and reduced the risk of patients developing metastases (22 *versus* 31 per cent). This latter effect was more marked in the group of patients with lymph node involvement by tumour (relapse-free survival was 71 *versus* 57 per cent). A subsequent study in patients with breast cancer evaluated the effect of PAPU in those with lymph node involvement by tumour[127]. A total of 517 patients underwent mastectomy and axillary surgery and were then randomized to receive chemotherapy for 6 months or pelvic radiotherapy and PAPU 60 mg intravenously once per week for 6 weeks. The 5-year overall survival rate was similar in both groups, but the relapse-free 5-year survival rate was significantly better in the group receiving radiotherapy and PAPU (57 *versus* 46 per cent). This suggests that PAPU is as effective as chemotherapy in terms of overall survival and more effective than chemotherapy in prolonging relapse-free survival.

Stomach cancer. In 1990, Youn and colleagues[128] reported the effects of PAPU treatment in patients with stomach cancer. A total of 224 patients was randomized to receive chemotherapy and PAPU 100 mg or chemotherapy alone, starting 10–15 days after gastrectomy. Patients receiving chemotherapy and PAPU had better overall survival and a reduced risk of recurrence compared with those who received chemotherapy alone.

Colonic cancer. The use of PAPU in colorectal cancer has not yielded favourable results[129]; 288 patients who had undergone resection for colorectal cancer were randomized to receive either PAPU 30 mg or placebo,

Table 5 Clinical and biological effect of polyribonucleotides

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Youn *et al.*[123]	1985	Stomach cancer	47	Patients underwent surgery followed by chemotherapy and were randomized to receive either PAPU or placebo	NK cell cytotoxicity increased in patients receiving PAPU
Khan *et al.*[124]	1995	Breast cancer	20	Patients randomized to receive either PAPU or placebo, starting 2 days before surgery and for 2 weeks after surgery	Increased NK cell cytotoxicity in the PAPU group compared with control patients after operation
Lacour *et al.*[125]	1980	Breast cancer	300	Patients randomized to receive PAPU or placebo after surgery for 6 weeks	Overall survival and disease-free survival increased in all patients, but particularly in those with lymph node involvement (mean follow-up 50 months)
Lacour *et al.*[126]	1984	Breast cancer	300	Same patients as above, but longer follow-up	Overall survival and disease-free survival increased in all patients but particularly in those with lymph node involvement (mean follow-up 87 months)
Lacour *et al.*[127]	1991	Breast cancer	517	Patients underwent mastectomy; randomized to PAPU and pelvic radiotherapy or to chemotherapy	Overall survival similar in both groups but increased 5-year relapse-free survival in patients receiving PAPU compared with chemotherapy group
Youn *et al.*[128]	1990	Stomach cancer	224	Patients received chemotherapy and either PAPU or placebo, starting 2–3 weeks after surgery, for 6 weeks	Increased relapse-free survival and overall survival in patients receiving PAPU; effects more marked in patients with involved lymph nodes
Lacour *et al.*[129]	1992	Colorectal cancer	288	Patients received either PAPU or placebo, starting 10–15 days after surgery, for 6 weeks	No difference in survival between patients receiving PAPU or placebo

PAPU, polyadenylic–polyuridylic acid; NK, natural killer starting 10–15 days after surgery, and repeated at intervals of 1 week for 6 weeks. After a follow-up of 78 months, survival was better in the placebo group than in the PAPU group. These findings are disappointing but other studies evaluating the role of biological response modifiers as single-agent adjuvant therapy in patients with colorectal cancer have also failed to demonstrate benefit[130,131].

Combinations of specific nutrients

Combinations of L-arginine, n-3 fatty acids and polyribonucleotides have been evaluated in patients undergoing surgery (*Table 6*). Daly *et al.*[132] have evaluated the effects of an enteral nutrition regimen supplemented with L-arginine (up to 34 g/day), RNA (up to 3 g/day) and n-3 fatty acids (EPA–DHA up to 5·3 g/day) compared with an isocaloric enteral regimen. The patients had surgery for upper gastrointestinal malignancy and then received one of the two feeding regimens from days 1 to 7 after operation. Those with a supplemented diet had increased lymphocyte responsiveness to mitogens and an improved nitrogen balance. A clinical benefit was observed in the supplemented group, which had a reduced incidence of wound complications, including wound infections. There was also a significant reduction in the mean hospital stay compared with that in the non-supplemented group (10 *versus* 15 days respectively). However, the nitrogen intake differed between the groups: mean intake was 15·6 g nitrogen per day in the supplemented group and 9·0 g nitrogen per day in the non-supplemented group.

Kemen and colleagues[133] studied 42 patients who had surgery for upper gastrointestinal cancer. The patients were randomized to receive an enteral diet supplemented with L-arginine (up to 24 g/day), RNA (2·3 g/day) and a combination of n-3 and n-6 fatty acids, or a standard isocaloric isonitrogenous diet. This commenced on the day after surgery and continued for 10 days. There was an increased number of T lymphocytes, T helper cells and activated cells in the supplemented, compared with the non-supplemented, group. In addition, immunoglobulin (Ig) G and IgM levels were increased in the supplemented group after surgery, but morbidity and mortality rates were not given.

Recently, a further study by Daly *et al.*[134] evaluated nutritional supplementation in patients with upper gastrointestinal and pancreatic cancers. Sixty patients were stratified according to weight loss and cancer site (upper gastrointestinal or pancreatic) and randomized to receive either a standard enteral nutrition regimen or a supplemented enteral diet (L-arginine up to 31 g/day, RNA up to 3 g/day, DHA–EPA up to 4·1 g/day) via a jejunostomy. This was commenced on the first postoperative day and continued until discharge from hospital. In addition, on discharge from hospital the patients were further randomized either to stop jejunostomy feeding or to continue with it for a further 12–16 weeks (when the patients were either recovering or receiving chemotherapy or radiotherapy). Those receiving the supplemented diet had an increased ratio of n-3 to n-6 fatty acids, both in plasma and cell membranes, and a reduction in the production of PGE$_2$. Importantly, only 10 per cent of patients with a supplemented diet had wound infection or other complication compared with 43 per cent in the non-supplemented group; hospital stay was shorter in the supplemented group than in those receiving a standard diet (16 *versus* 22 days). Finally, there were fewer readmissions following discharge in the supplemented group[134].

Conclusions

Selected nutrients have a significant effect on cell metabolism and growth, tissue repair and regeneration,

Table 6 Clinical and biological effect of combinations of specific nutrients

Reference	Year	Patient group	No. of patients	Protocol	Outcome
Daly *et al.*[132]	1992	Gastrointestinal malignancy	85	After surgery, received either standard enteral diet or diet supplemented with L-arginine, ω-3 fatty acids and ribonucleotides for 7 days	Patients in supplemented group had a better nitrogen balance, enhanced *in vitro* lymphocyte responses to mitogens, fewer infections and wound complications, and shorter hospital stay
Kemen *et al.*[133]	1995	Gastrointestinal malignancy	42	After surgery, received either a standard diet or diet supplemented with L-arginine, n-3 fatty acids and ribonucleotides for 10 days after operation	Patients in the supplemented group had increased numbers of T cells, CD4-positive (T helper) and activated T cells, and increased IgM, IgG and IFN-γ levels. Effects on complications and clinical outcome unclear
Daly *et al.*[134]	1995	Upper gastrointestinal and pancreatic cancer	60	After surgery, patients randomized to standard enteral nutrition or enteral nutrition and supplementation (L-arginine, n-3 fatty acids and ribonucleotides)	Reduced wound infections and complications and shorter hospital stay in the supplemented group compared with the non-supplemented group (10 *versus* 43 per cent; 16 *versus* 22 days respectively)
Cerra *et al.*[135]	1990	Intensive care patients*	20	Patients randomized to receive either an enteral diet supplemented with L-arginine, ω-3 fatty acids and ribonucleotides or a standard diet for 7–10 days	*In vitro* tests of lymphocyte function (responses to mitogens) were enhanced in patients with a supplemented diet; there were no differences in clinical outcome or length of ICU stay

*Six patients in this group with sepsis had undergone oesophagogastrectomy. Ig, immunoglobulin; IFN, interferon; ICU, intensive care unit and modulation of host defences, but possible clinical benefits are difficult to demonstrate. Patient numbers in the studies published to date have generally been small and the clinical benefits variable. The use of combinations of nutrients appears more promising, with some reports of significant advantages (reduction in infectious complications and a shortening of hospital stay). Other potentially beneficial applications of nutritional pharmacology to clinical practice are the possibility of increasing tumour response to chemotherapeutic agents and minimizing the metabolic effects of cachexia. Further work is necessary to evaluate more fully the role of selected nutrients in malignant disease.

Acknowledgements

The authors are grateful to the Scottish Hospitals Endowment Research Trust for financial help.

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Announcement

European Surgical Fellowships

Council of The British Journal of Surgery Society is pleased to announce the availability of the first tranche of European Surgical Fellowships for 1996.

Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the United Kingdom to visit centres in other European countries, or surgeons working in other European countries to visit the United Kingdom. Applicants must be under 40 years of age and should submit details of their proposed itinerary, its anticipated cost, a copy of their curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 28 June 1996.

J. R. C. Sainsbury

British Journal of Surgery 1996, 83, 620–624

Assessment of splanchnic tissue oxygenation by gastric tonometry in patients undergoing laparoscopic and open cholecystectomy

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This experimental study compared the effects of laparoscopic ($n = 31$) and open ($n = 32$) cholecystectomy on gastric intramucosal pH ($\mathrm{pH_i}$). For this purpose, $\mathrm{pH_i}$ was measured tonometrically before induction of anaesthesia, at 30-min intervals during surgery, and 1, 2 and 4 h after operation in otherwise healthy patients undergoing elective cholecystectomy. Additionally, perioperative arterial pH ($\mathrm{pH_a}$), arterial carbon dioxide tension ($P_{\mathrm{aCO_2}}$), intramucosal carbon dioxide tension, arterial bicarbonate concentration, end-tidal carbon dioxide pressure ($P_{\mathrm{ECO_2}}$), levels of serum lactate, lactate dehydrogenase (LDH) and γ-glutamyl transferase (GGT), haematocrit and arterial blood pressure were recorded. In the two groups no significantly different changes occurred in $\mathrm{pH_i}$, $\mathrm{pH_a}$, serum lactate concentration or haematocrit at any of the observation times. $P_{\mathrm{ECO_2}}$ and $P_{\mathrm{aCO_2}}$ were significantly raised during the laparoscopic procedure, whereas levels of LDH and GGT and arterial blood pressure rose during and after open cholecystectomy. In spite of the increased intra-abdominal pressure and the peritoneal carbon dioxide absorption related to the creation of a pneumoperitoneum, no decrease in $\mathrm{pH_i}$ was detectable during laparoscopic cholecystectomy.

Over the past few years laparoscopic cholecystectomy has become a widely practised procedure in Europe and the USA. Potential benefits claimed for the procedure are smaller incisions, shortened periods of hospitalization, decreased postoperative pain and cost-effectiveness[1]. There is an implicit assumption that laparoscopic cholecystectomy is less invasive than open cholecystectomy and produces fewer overall physiological derangements.

Laparoscopic cholecystectomy requires peritoneal gas insufflation to provide adequate visualization and exposure. Usually carbon dioxide is used as the insufflating agent because it is readily available, does not support combustion and is chemically stable. Until the advent of extended therapeutic procedures such as laparoscopic cholecystectomy, most laparoscopies were brief and performed in young women. Pathophysiological alterations due to pneumoperitoneum have been studied extensively and found to be clinically irrelevant[2–4].

With the increasing popularity of minimally invasive general surgery, many laparoscopic procedures now require lengthy periods of peritoneal insufflation and are often performed in patients who are older and suffer from cardiac and pulmonary disease. Several experimental and clinical studies have been carried out to assess cardiocirculatory, respiratory and endocrine responses in patients undergoing laparoscopic cholecystectomy[5–12]. Raised intra-abdominal pressure is associated with a decrease in abdominal visceral organ blood flow, as shown with radioactive microspheres[13] or by measuring the intramucosal pH ($\mathrm{pH_i}$) tonometrically[14]. At an intra-abdominal pressure of 20 mmHg a mucosal pH of 7·16 was found, and at 40 mmHg the $\mathrm{pH_i}$ fell further to 6·98. Decreases in splanchnic blood flow, with an associated reduction in gut perfusion, can result in tissue hypoxia, anaerobic glycolysis and tissue acidosis. These alterations are reflected in the intestinal and gastric mucosa by increases in the tissue concentrations of hydrogen ions and carbon dioxide. The putative consequences of intramucosal acidosis and associated mucosal injury include bacterial translocation, nosocomial pneumonia, myocardial depression, sepsis, multisystem organ failure and death[15]. Since the gut has been identified as the 'motor of multiple system organ failure'[16], intestinal mucosal changes have been carefully investigated in many circumstances.

To date, in experimental studies[13,14] intra-abdominal pressure has been increased by infusion of saline or Ringer's lactate into the peritoneal cavity instead of carbon dioxide insufflation, and splanchnic blood flow during laparoscopic cholecystectomy has yet to be investigated. Its determination by means of a gastrointestinal tonometer[17] is a reliable and non-invasive method which can be carried out safely in patients undergoing cholecystectomy. The present study assessed the intramucosal pH by gastric tonometry during laparoscopic cholecystectomy; patients treated by open cholecystectomy were used as a control group.

Patients and methods

The study was approved by the local hospital ethics committee. Written informed consent was obtained from all patients.

Only patients undergoing elective cholecystectomy were considered for entry to the trial. Patients with acute cholecystitis, cholangitis and pancreatitis, as well as those with cardiopulmonary disease, portal hypertension and haemostatic disorders, were excluded. Since laparoscopic cholecystectomy is the method of choice for patients who have to be operated on electively[18], only those with a contraindication for the laparoscopic procedure were eligible for open cholecystectomy. Therefore, 15 patients with a contracted thickened gallbladder, nine with previous upper abdominal surgery, five with suspected or proven biliary duct stones, and three with suspected malignancy were treated by open cholecystectomy. A prospective randomized study, although desirable, proved impossible to implement for these reasons.

Presented to the Third International Congress on New Technology and Advanced Techniques in Surgery in Luxembourg, 11–17 June 1995

Paper accepted 6 September 1995

All patients were informed about the advantages and possible complications of the laparoscopic *versus* the open procedure, and about the reason for assignment to one of the two treatment modalities. These decisions were not influenced by the study design. Seventy otherwise healthy patients scheduled for elective cholecystectomy participated in the study. Of these, seven were excluded because of equipment failure and lack of skilled personnel. Thirty-one patients undergoing laparoscopic cholecystectomy and 32 having the open procedure (*Table 1*) were available for evaluation.

Patients underwent total intravenous general anaesthesia with propofol for induction (2 mg kg^{-1}) and maintenance (5–10 mg kg^{-1} h^{-1}), fentanyl for analgesia (2 μg kg^{-1} h^{-1}) and vecuronium (0·1 mg kg^{-1}) for muscle relaxation. A Siemens Servo Ventilator 900/900B (Siemens Elema, Solna, Sweden) was used.

End-tidal carbon dioxide tension (P_{ECO_2}) was measured throughout the operation using a Hewlett-Packard (model 66S) infrared analyser (Hewlett-Packard, Vancouver, Washington, USA). Minute ventilation was adjusted to obtain P_{ECO_2} within the range. At 1 h before operation patients received 2 g mezlocillin and 40 mg ranitidine with the premedication. Thereafter the tonometry catheter (TRIP NGS Catheter; Tonometrics, Worcester, Massachusetts, USA.) was placed in the stomach by a transnasal route and the balloon was filled with 2·5 ml saline. The correct positioning of the tonometer was confirmed by auscultation and aspiration of bile.

pH_i was measured immediately before induction of anaesthesia, 30 min after peritoneal insufflation or laparotomy, every 30 min up to the end of the operation, and finally 1, 2 and 4 h after surgery. Arterial blood pressure was recorded at the same time points. Haemoglobin, haematocrit, serum lactate, lactate dehydrogenase (LDH), γ-glutamyl transferase (GGT) levels and arterial blood pressure were measured before operation, 30 min after the start of operation, 2 h after operation and on postoperative day 1. Arterial pH (pH_a), arterial carbon dioxide tension (P_{aCO_2}), gastric intramucosal carbon dioxide tension (P_{iCO_2}) and arterial bicarbonate concentration were recorded at the same time points as for pH_i measurement.

Table 1 Preoperative patient details

	Laparoscopic cholecystectomy ($n = 31$)	Open cholecystectomy ($n = 32$)
Sex ratio (F:M)	27:4	23:9
Mean(s.d.) age (years)	41·9(11·2)	58·3(11·4)*
Mean(s.d.) weight (kg)	67·3(11·8)	71·1(13·0)

*$P < 0·05$ (analysis of variance)

Laparoscopic cholecystectomy was performed using four cannulas, with the patient in a 30° head-down tilt during carbon dioxide insufflation and in a 15–20° head-up tilt after insertion of the cannulas. Intra-abdominal pressure was maintained continuously at 15 mmHg with the Laparoflator Electronic 3509 (Wiest, Unterhaching, Germany). Laparoscopic cholecystectomy was performed with a standard technique. In patients undergoing laparoscopic cholecystectomy, intravenous cholangiography was performed routinely before operation. The open procedure was performed through a standard subcostal incision, and in these cases intraoperative cholangiography was routine practice.

Statistical analysis

Data are reported as means(s.d.) and as mean (95 per cent confidence interval (c.i.)). Continuous data were compared by analysis of variance. Between-group significance levels were assessed using the Scheffé *post hoc* test with the Bonferroni correction. The level of significance was set at $P < 0·05$.

Biochemical assays

To estimate pH_a and P_{aCO_2} as well as P_{CO_2} in saline (P_{iCO_2}) the Radiometer ABL 500 blood gas analyser (Radiometer, Copenhagen, Denmark) was used. Lactate concentration was measured with a fluorescence polarization immunoassay method (TDxFLx; Abbott Laboratories, Chicago, Illinois, USA). LDH and GGT serum concentrations were determined enzymatically with a Bayer Technicon Dax System 96 analyser (Technicon, Tarrytown, New York, USA). Haematocrit was measured by direct electronic optical count with the Bayer Technicon H2 device (Technicon).

Tonometry

The tonometer consists of a silicone balloon that is freely permeable and a sampling tube that is impermeable to carbon dioxide. Gastric intramucosal pH is estimated by determining the P_{CO_2} of fluid within the balloon and inserting this value (corrected for temperature and dwell time) in the Henderson–Hasselbach equation:

$$pH = 6·1 + \log [HCO_3^-]/(P_{CO_2}) \times 0·03$$

where $[HCO_3^-]$ is the simultaneous concentration of bicarbonate in arterial blood. Intraluminal production of carbon dioxide from the titration of gastric acid by secreted bicarbonate can result in an underestimation of gastric intramucosal pH by tonometry, a phenomenon that is offset by H_2-receptor blockade with ranitidine[19]. The principle of determining pH_i tonometrically is based on two assumptions: (1) P_{CO_2} in the lumen of a hollow viscus is

Table 2 Changes in arterial carbon dioxide tension, end-tidal carbon dioxide pressure, and arterial and intramucosal pH after intraperitoneal carbon dioxide insufflation

	Before operation	60 min after insufflation
P_{aCO_2} (mmHg)		
Laparoscopic cholecystectomy	36·4 (34·6–38·2)	44·5* (43·2–45·9)
Open cholecystectomy	36·4 (34·5–38·2)	40·2 (38·8–41·6)
P_{ECO_2} (mmHg)		
Laparoscopic cholecystectomy	29·6 (28·6–30·6)	37·3* (36·4–38·1)
Open cholecystectomy	30·9 (29·7–32·3)	32·4 (31·2–33·8)
Arterial $[H^+]$ (nmol l^{-1})		
Laparoscopic cholecystectomy	40 (38–42)	47* (45–48)
Open cholecystectomy	37 (35–39)	41 (39–43)
Intramucosal $[H^+]$ (nmol l^{-1})		
Laparoscopic cholecystectomy	47 (45–49)	48 (46–50)
Open cholecystectomy	43 (40–47)	46 (44–48)

Values are mean (95 per cent confidence interval). P_{aCO_2}, arterial carbon dioxide tension; P_{ECO_2}, end-tidal carbon dioxide pressure; $[H^+]$, hydrogen ion concentration. *$P < 0·05$ *versus* before operation (analysis of variance)

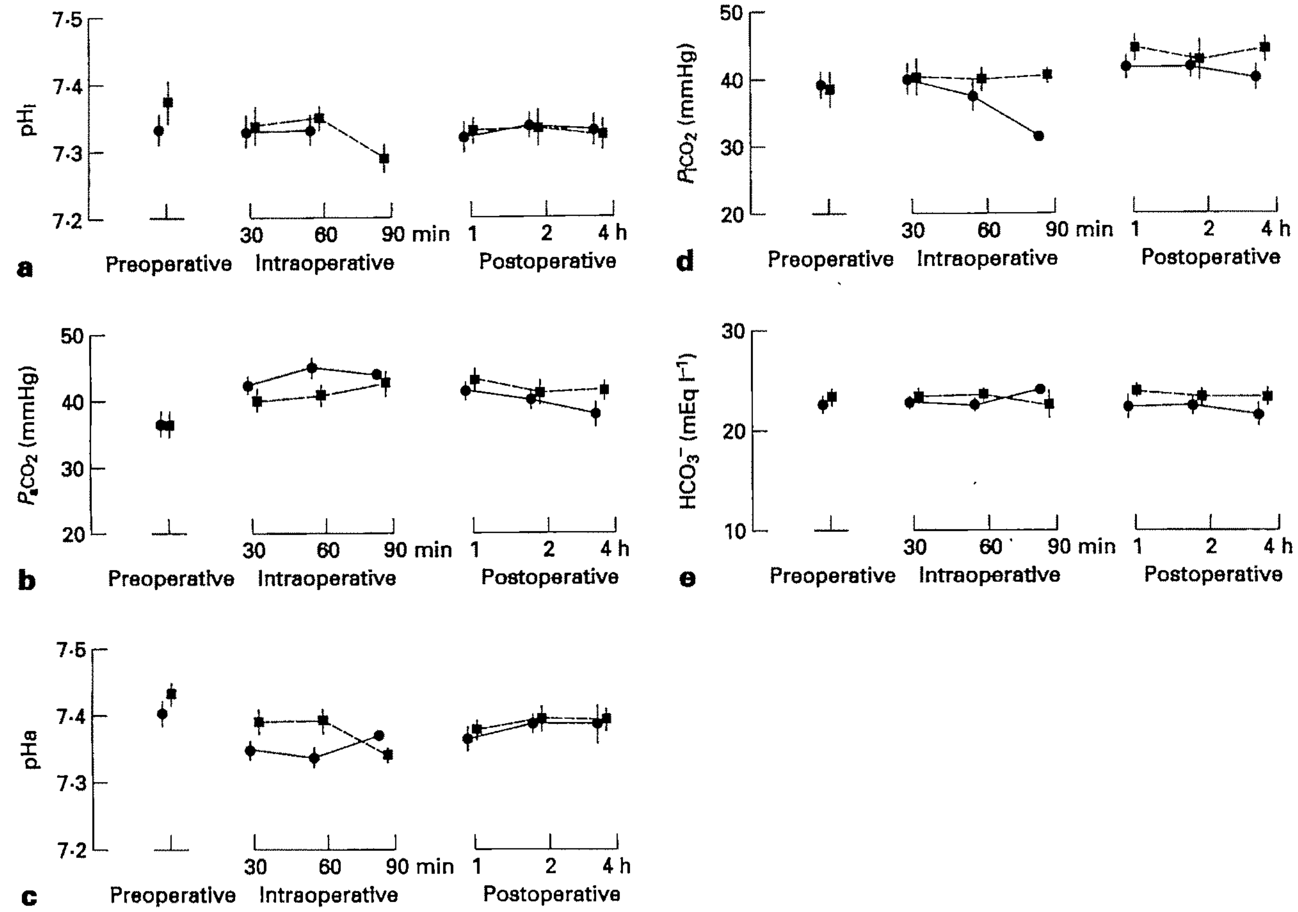

Fig. 1 Changes in a intramucosal pH (pH$_i$), b arterial carbon dioxide tension ($P_{a\mathrm{CO}_2}$), c arterial pH (pH$_a$), d intramucosal carbon dioxide tension ($P_{i\mathrm{CO}_2}$) and e arterial bicarbonate (HCO_3^-) concentration in patients subjected to laparoscopic (●) and open (■) cholecystectomy. Values are mean (95 per cent confidence interval)

Table 3 Changes in serum lactate dehydrogenase concentration in patients undergoing laparoscopic and open cholecystectomy

	Laparoscopic cholecystetomy	Open cholecystectomy
Lactate dehydrogenase (units l^{-1})		
Before operation	258·2 (236·3–280·0)	280·3 (256·8–303·8)
During operation	271·3 (242·3–300·3)	343·5* (299·7–387·4)
After operation	272·3 (244·7–299·9)	365·1* (309·7–420·5)
On postoperative day 1	260·7 (237·9–283·4)	336·5* (290·2–382·7)

Values are mean (95 per cent confidence interval). *$P < 0.05$ (open *versus* laparoscopic cholecystectomy, analysis of variance)

the same as that of its wall; and (2) tissue bicarbonate concentration equals that of arterial blood.

Results

The two groups were similar in number, mean weight and sex distribution, but differed in terms of patient age. The two groups were well matched for mean preoperative arterial blood pressure, blood gas values and concentrations of plasma substrates.

Depending on the operating time, tonometric measurements were performed in all patients at 30 min,

Table 4 Changes in serum γ-glutamyl transferase concentration in patients undergoing laparoscopic and open cholecystectomy

	Laparoscopic cholecystectomy	Open cholecystectomy
γ-Glutamyl transferase (units l^{-1})		
Before operation	24·7 (13·9–35·5)	56·6* (27·9–85·2)
During operation	23·6 (16·9–37·4)	60·6* (33·3–87·9)
After operation	24·4 (16·5–32·4)	52·6* (28·2–77·0)
On postoperative day 1	22·2 (15·7–28·7)	54·2* (33·2–75·3)

Values are mean (95 per cent confidence interval). *$P < 0.05$ (open *versus* laparoscopic cholecystetomy, analysis of variance)

Table 5 Changes in mean arterial blood pressure in patients subjected to laparoscopic and open cholecystectomy

	Laparoscopic cholecystectomy	Open cholecystectomy
Arterial blood pressure (mmHg)		
Before operation	107 (104–110)	108 (102–113)
During operation	104 (100–108)	104 (98–111)
After operation	99 (94–104)	108* (104–112)
On postoperative day 1	97 (95–103)	106* (101–111)

Values are mean (95 per cent confidence interval). *$P < 0.005$ (open *versus* laparoscopic cholecystectomy, analysis of variance) but in only 17 at 60 min and in four at 90 min during operation.

pH_i did not decrease during laparoscopic cholecystectomy and was not significantly different in the two groups at any time (*Table 2*; *Fig. 1a*). In the case of laparoscopic cholecystectomy, induction of a carbon dioxide pneumoperitoneum resulted in a progressive rise in P_{aCO_2} (*Table 2*; *Fig. 1b*) and P_{ECO_2} (*Table 2*) and a decrease in pH_a (*Table 2*; *Fig. 1c*). The differences were statistically significant, but the mean values were within the normal range. P_{iCO_2} (*Fig. 1d*), bicarbonate concentration (*Fig. 1e*) and serum lactate levels showed no significant changes.

Open cholecystectomy was associated with a rise in serum LDH (*Table 3*) and GGT (*Table 4*) concentrations. Serum haematocrit remained stable in both groups, and arterial blood pressure (*Table 5*) rose significantly after open cholecystectomy.

The mean duration of surgery was similar in the two groups (68 *versus* 71 min). There were no operative complications. Patients were discharged a mean of 3 days after laparoscopic and 8 days after open cholecystectomy.

Discussion

Estimation of gastric intramucosal pH based on the assumption that the bicarbonate concentration of the stomach wall and of arterial blood are the same is not generally accepted. The tonometric method for measuring gastrointestinal pH is not reliable under conditions of zero flow and leads to errors under conditions of low flow, as has been shown during haemorrhagic and septic shock[20,21]. Tonometrically estimated gut pH_i and pH_i measured directly with microelectrodes correlated well in healthy pigs and in porcine endotoxic shock[22]. Therefore, in patients with American Society of Anesthesiologists grade I and II undergoing laparoscopic or open cholecystectomy without complications, gastric intramucosal and arterial bicarbonate concentrations are presumably equal and tonometric assessment of gastric pH_i appears to be a reliable method[23].

The present study demonstrated no significant response of pH_i to laparoscopic or open cholecystectomy. The expected decrease in pH_i during laparoscopic cholecystectomy was not observed. In otherwise healthy patients, an increased intra-abdominal pressure of up to 15 mmHg had no adverse effect on the splanchnic intramucosal gastric pH. Although peritoneal carbon dioxide absorption was associated with a decrease in pH_a and an increase in P_{aCO_2} and P_{ECO_2}, no tissue acidosis developed in the gastric mucosa.

The concentration of serum lactate, a sensitive indicator of anaerobic metabolism, did not rise at any time, but measurement of lactate levels in the portal vein or in central venous blood would have been more useful for the present purposes. An increase in liver enzyme serum levels may have been caused by the abdominal wall incision rather than by splanchnic ischaemia, or else resulted from increased intrabiliary pressure caused by the injection of radiological contrast medium. There was, however, no significant difference in inflammation between the two groups of patients, as indicated by histological examination of the gallbladder or bacteriological examination of the bile.

The rise in arterial blood pressure after operation in patients who had open cholecystectomy was probably caused by pain. Although laparoscopic cholecystectomy usually takes longer to perform than the open procedure, routine intraoperative cholangiography in the latter was the reason why the operating time was similar for the two procedures.

It is concluded that, in patients without cardiopulmonary disease, neural and humoral systemic mechanisms as well as intact splanchnic ‘autoregulation’[24] are capable of counteracting the adverse effects of carbon dioxide pneumoperitoneum during laparoscopic cholecystectomy to a degree that is not detectable by tonometry, a highly sensitive method for assessing intramucosal pH. This implies that laparoscopic operations have no adverse effect on gut perfusion in otherwise healthy patients. The study shows that tonometry is a safe and non-invasive method for measuring gastric mucosal pH. There were no tonometry-related complications. Although it is a reliable and clinically practicable method, tonometry cannot be applied routinely during laparoscopic procedures. Its use in patients with cardiac and/or respiratory diseases may be of interest.

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Announcement

Association of Gastrointestinal Surgeons of Great Britain and Ireland

This new Association will be formed under the umbrella of the Association of Surgeons of Great Britain and Ireland (ASGBI) and at the request of many of the Fellows of that Association. It will embrace the science and practice of surgery of the oesophagus, stomach, duodenum, jejunoileum, liver, gallbladder, biliary tree, pancreas, portal vein and spleen. As general surgery in Britain ramifies into groupings such as vascular, breast, endocrine, transplant surgery and coloproctology, so each is developing its own professional organization. The new Association of Gastrointestinal Surgeons is created to represent those with either an oesophagogastric or an HPB (hepatopancreatobiliary) interest, since it is anticipated that these two disciplines will remain closely linked for the foreseeable future. The Association will provide a structure for education and training, clinical developments and research into some of the most challenging diseases that confront surgeons today. Support, both practical and conceptual, has been offered by the Royal Colleges of Surgeons and the ASGBI, as well as by the leading experts in the field.

A Steering Group was established in 1995 to help bring the Association of Gastrointestinal Surgeons into being, to prepare a draft constitution and to arrange an inaugural meeting for more detailed discussion of aims and activities. This meeting will take place during the Annual Meeting of the ASGBI in Glasgow on the morning of Thursday 23 May 1996, with the following title and programme. We urge all those with an interest in the specialty to attend.

Gastrointestinal Surgery: Junctional Zones
10.30–12.15 hrs, 23 May 1996, Glasgow, UK

1 Scientific Update	
Zenker's diverticulum and the cricopharyngeus	T. N. Walsh
Splenectomy in the operative treatment of gastric cancer	D. Johnston
Papillary stenosis	R. C. G. Russell
Re-resection for hepatic metastases	M. Rees
2 Birth of the Association: live or still?	
Rationale and draft constitution	Steering Group

W. H. Allum
J. Bancewicz
G. Glazer
A. Watson
R. C. N. Williamson

British Journal of Surgery 1996, **83**, 625–631

Survival after resection for ductal adenocarcinoma of the pancreas

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A retrospective study was performed of 113 patients who underwent surgical resection of carcinoma of the pancreas from 1970 to 1992. The postoperative mortality rate was 15 per cent (5 per cent in the last 11 years). The actuarial 5-year survival rate was 12 per cent. Survival was significantly influenced by age (P = 0·03), vascular resection (P = 0·02), radicality of operation (P = 0·01), number of transfused blood units (P = 0·01), tumour differentiation (P = 0·002), lymph node status (P = 0·001), perineural invasion (P = 0·01), tumour size (P = 0·008), preoperative diabetes (P = 0·001) and stage (P = 0·0001). Multivariate analysis showed that stage, diabetes, age and grade were independent predictors of long-term survival. The type of pancreatic resection (Whipple, subtotal, total or distal pancreatectomy) did not influence prognosis. The 5-year survival rate was 14 per cent in the period 1970–1981 and 11 per cent in the period 1982–1992, with no statistical difference. These results suggest that patient characteristics and tumour findings rather than operative procedures affect long-term survival after resection for pancreatic carcinoma.

Pancreatic cancer continues to be a great challenge for surgeons and oncologists, since it is the fourth leading cause of cancer death in the USA[1] and the sixth in Italy[2]. Resection has been advocated as the only chance of cure for this disease[3], but problems related to surgical resection of pancreatic carcinoma still remain: high operative risk; choice of surgical procedure; and poor 5-year survival rate[4,5]. However, a significant decrease in mortality and morbidity rates has been reported recently by several specialized centres[6–8], together with an encouraging 5-year survival rate: 24 per cent reported by Trede *et al.*[8] and 21 per cent by Cameron and co-workers[9]. Interestingly, in the same series, patients with no residual tumour after resection had a 5-year survival rate of 36 per cent[8] and those without lymph node metastases had a 57 per cent survival rate at 5 years[9].

In the present study a 23-year experience of surgical resection for pancreatic carcinoma was reviewed to evaluate early and late results, and the eventual progress of this surgery in recent years. Clinicopathological factors related to prognosis were also analysed and data collected from recent published series were reviewed.

Patients and methods

In the authors' department, from 1970 to 1992, 113 patients (21 per cent) underwent pancreatic resection of a total of 549 with histologically proven pancreatic adenocarcinoma. Patients with cystadenocarcinoma, tumours of the endocrine pancreas, and cancer of the bile duct, duodenum or ampulla of Vater were excluded from the study. Surgical resection was performed whenever it was technically possible and when no distant metastases were identified. Limited invasion of portal and/or mesenteric vein were not considered a contraindication for pancreatic resection. At the time of surgery, pancreatic carcinoma was staged following the tumour node metastasis (TNM) system of the Union Internacional Contra la Cancrum (UICC)[10]. Mortality was defined as any death occurring before discharge from the hospital. A pancreatic fistula was diagnosed if significant leakage of amylase-rich fluid occurred.

To show trends in mortality, morbidity and survival, patients were divided into two periods of observation: 1970–1981 and 1982–1992. The two groups of patients were comparable for age, sex distribution, associated medical illness, preoperative laboratory data and pathological features of the tumour. Forty-nine operations were performed in the first period and 64 in the second.

A total of 77 patients underwent pancreaticoduodenectomy, 13 total pancreatectomy and 23 left pancreatectomy. In 14 patients a segmental portal and/or mesenteric vein resection was also performed: seven after pancreaticoduodenectomy, six after total pancreatectomy and one after left pancreatectomy. Pylorus-preserving pancreatectomy was performed in 14 patients (13 after panceaticoduodenectomy and one after total pancreatectomy); in three of these patients vascular resection was also done. Nine of 13 total pancreatectomy and nine of 14 vascular resections were performed from 1970 to 1981; four total pancreatectomies, five vascular resections and all pylorus-preserving pancreatectomies were performed from 1982 to 1992.

From 1982 pancreaticoduodenectomy was performed by dividing the pancreas 2 cm to the left of the origin of the splenic artery, leaving a distal pancreatic stump approximately 4–5 cm long, with spleen preservation. This procedure (so-called subtotal pancreaticoduodenectomy) allows a more accurate lymphadenectomy of the body of the pancreas. Thirty-six patients underwent the standard Whipple resection and 41 subtotal pancreaticoduodenectomy.

Histological slides and resected specimens were reviewed to confirm the diagnosis and to study the following pathological features, potentially able to influence prognosis: size and grading of the tumour, nodal status and margin, vascular invasion, microscopic involvement of perineural spaces, and lymphatic and blood vessels. Other determinant variables analysed included age, sex, diabetes, type of resection, radicality of operation and perioperative blood transfusion.

Follow-up of the patients included clinical evaluation, routine laboratory tests 1 month after operation, and then abdominal ultrasonography and/or computed tomography (CT) (when available) and chest radiography every 3 months. Complete follow-up was obtained in 112 patients. No patient was treated with adjuvant radiotherapy or chemotherapy. Causes of death were recorded on the basis of death certification, medical interview and autopsy.

Actuarial survival curves were prepared using the Kaplan–Meier method and statistical comparisons were made by the generalized Wilcoxon (Breslow) test. A Cox proportional hazards analysis was used to determine which independent variables influenced survival. $P < 0·05$ was considered significant.

Results

There were 66 men and 47 women of mean age 59·4 (range 27–81) years. Detailed clinical data are shown in

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Table 1. The tumour was located in the head of the gland in 86 patients, in the body and tail in 23 and in the whole pancreas in four. Mean tumour diameter was 3·4 (range 1·0–10·0) cm; in 20 patients the tumour size was 2 cm or less, in 66 it was 2·1–4·0 cm and in 27 it was greater than 4 cm. There were 55 well differentiated, 39 moderately differentiated and 19 poorly differentiated tumours. Fifty patients had lymph node metastases. In 19 patients (17 per cent; nine pancreaticoduodenectomy and ten distal pancreatectomy) the resection was not considered radical (R_1) for the following reasons: macroscopic tumour remnants ($n = 9$), or microscopic involvement of the portal vein ($n = 2$), line of resection ($n = 5$) or peripancreatic tissue ($n = 3$), thus leaving insufficient free margins.

In three patients who had distal pancreatectomy, macroscopic involvement of adjacent organs required *en bloc* resection of stomach and colon. According to the TNM staging system, 46 patients were at stage I, 17 at stage II and 50 at stage III. Twenty-five (54 per cent) of patients with stage I tumours were operated on in the period 1970–1981 and 21 (46 per cent) in 1982–1993. The resectability rate was 15 per cent (49 of 321) in the first period and 28 per cent (64 of 228) in the second period. Major postoperative complications were registered in 45 patients (40 per cent) and are listed in *Table 2*. The most frequent complication was pancreatic fistula (13 patients; 29 per cent) after pancreaticoduodenectomy. Nine pancreatic fistulas occurred between 1970 and 1981 with two reoperations, while four cases were recorded in the second period (all were treated conservatively). Other complications included intra-abdominal abscess in 11 patients, biliary fistula in three and digestive bleeding in four. Nine patients required reoperation. Morbidity occurred in 43 per cent (33 of 77) after pancreaticoduodenectomy, 54 per cent (seven of 13) after total pancreatectomy, 22 per cent (five of 23) after left pancreatectomy, 43 per cent (six of 14) after vascular resection and 36 per cent (five of 14) after pylorus-preserving pancreatectomy. Complications were recorded in 49 per cent of patients who underwent standard Whipple resection and in 37 per cent of those who had subtotal pancreaticoduodenectomy.

Table 1 Characteristics of patients undergoing resection for adenocarcinoma of the pancreas

	Whipple	SPD	TP	DP
Mean age (years)	57·1	61·0	55·1	60·6
Sex ratio (M:F)	24:12	23:18	6:7	13:10
UICC stage				
I	20	15	4	7
II	1	3	3	10
III	15	23	6	6
Differentiation				
Well	19	14	9	13
Moderate	13	16	3	7
Poor	4	11	1	3
Vein resection				
Yes	1	6	6	1
No	35	35	7	22
Radicality				
Yes	32	36	13	13
No	4	5	0	10

SPD, subtotal pancreaticoduodenectomy; TP, total pancreatectomy; DP, distal pancreatectomy; UICC, Union International Contra la Cancrum

Seventeen patients died after operation, with an overall mortality rate of 15 per cent; 12 died after pancreaticoduodenectomy, in three of whom a pancreatic leak was documented. The mortality rate was 28 per cent (ten of 36) after Whipple operation and 5 per cent after subtotal pancreaticoduodenectomy (two of 41). Three patients died after total pancreatectomy (all as a result of intra-abdominal abscess) and two after left pancreatectomy (both with intra-abdominal sepsis). The mortality rate was 21 per cent (three of 14) in the group of patients who underwent vascular resection and nil after the pylorus-preserving operation.

Operative morbidity and mortality rates were 51 per cent (25 of 49) and 29 per cent (14 of 49) respectively in

Table 2 Operative morbidity according to type of resection

Complication	Whipple	SPD	TP	DP
Anastomotic leak				
Pancreaticojejunal	9 (3)	4	0	0
Gastrojejunal	1	0	0	0
Duodenojejunal	0	1	0	0
Abdominal abscess	3 (2)	0	5 (3)	3 (2)
Digestive bleeding	2 (1)	1	1	0
Peritoneal bleeding	0	3 (2)	0	0
Biliary fistula	2	0	1	0
Colonic perforation	1	0	0	1
Cardiac failure	2 (2)	0	0	0
Pneumonia	1 (1)	0	0	1
Liver failure	1 (1)	0	0	0
Renal failure	0	1	0	0
Intestinal obstruction	0	1	0	0
Total	22 (10)	11 (2)	7 (3)	5 (2)

Values in parentheses represent operative deaths. SPD, subtotal pancreaticoduodenectomy; TP, total pancreatectomy; DP, distal pancreatectomy

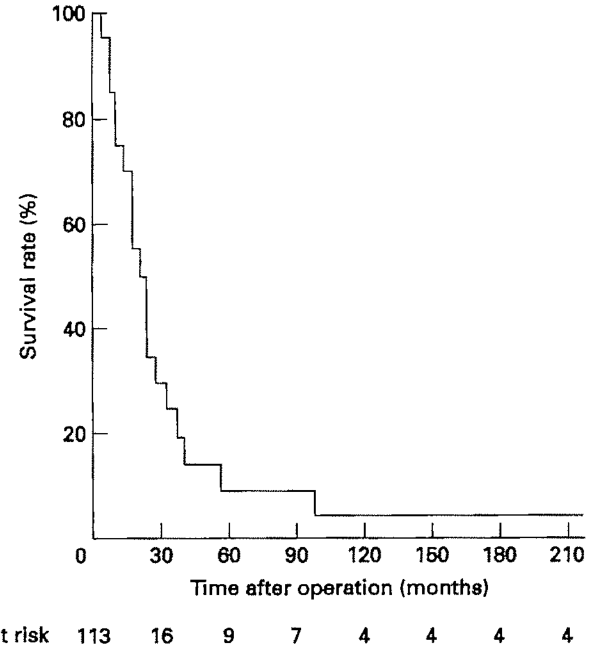

Fig. 1 Cumulative actuarial survival rate for 113 patients who underwent resection for pancreatic adenocarcinoma

the period 1970–1981, and 31 per cent (20 of 64) and 5 per cent (three of 64) in the period 1982–1992. Excluding hospital mortality, overall 1-, 3- and 5-year actuarial survival rates were 80, 22 and 12 per cent (*Fig. 1*).

Long-term survival was not related to sex, partial *versus* total pancreatectomy, pylorus preservation *versus* antrectomy, Whipple *versus* subtotal pancreaticoduodenectomy, or microscopic invasion of lymphatic and blood vessels (*Table 3*). Blood transfusion did not influence long-term survival; however, the actuarial survival rate was significantly lower for patients receiving more than 5 units of blood ($P = 0{\cdot}01$). Survival was

Table 3 Survival according to risk factors

Risk factor	No. of patients	Survival rate (%) 1 year	3 years	5 years	Median survival (months)	*P**
Age (years)						
<60	51	78	28	22	17	
60–69	46	86	17	4	13	0·03
≥70	16	71	14	0	7	
Sex ratio (M:F)	66:47	77:85	26:17	12:11	16:14	0·53
Operation						
PD	77	79	21	10	16	
TP	13	83	33	16	11	0·74
DP	23	83	23	23	11	
Vascular resection						
Yes	14	69	23	0	11	0·02
No	99	82	24	14	21	
Type of resection (extension to right side)						
Antrectomy	63	86	16	0	15	0·95
PPPD	14	78	26	10	16	
Type of resection (extension to left side)						
Whipple	36	83	25	12	14	0·30
Subtotal	41	75	16	0	13	
Radical resection						
Yes	94	79	26	15	14	0·01
No	19	84	6	0	7	
Blood transfusion (units)						
≤2	32	92	37	18	27	
3–5	46	78	16	12	12	0·01
>5	20	71	0	0	8	
Differentiation						
Well	55	91	37	18	20	
Moderate	39	71	3	3	9	0·002
Poor	19	62	14	0	7	
Lymph nodes						
Positive	50	68	5	0	8	0·001
Negative	63	90	35	19	22	
Lymphatic invasion						
Yes	66	78	13	7	15	0·17
No	47	84	36	19	18	
Vessel invasion						
Yes	44	80	19	13	14	0·60
No	69	82	24	10	19	
Nerve invasion						
Yes	71	73	11	7	14	0·01
No	42	92	35	18	24	
Peripancreatic invasion						
Yes	79	77	18	8	14	0·05
No	34	88	30	19	22	
Tumour size (cm)						
≤2	20	79	56	40	27	
2·1–4·0	66	81	18	8	16	0·008
>4·0	27	77	10	5	9	
Diabetes						
Yes	62	81	4	2	13	0·001
No	51	80	44	24	24	
UICC stage						
I	46	94	45	26	22	
II	17	77	8	0	11	0·0001
III	50	69	5	0	8	

PD, pancreaticoduodenectomy; TP, total pancreatectomy; DP, distal pancreatectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; UICC, Union Internacional Contra la Cancrum. *Kaplan–Meier analysis; curves compared with generalized Wilcoxon test

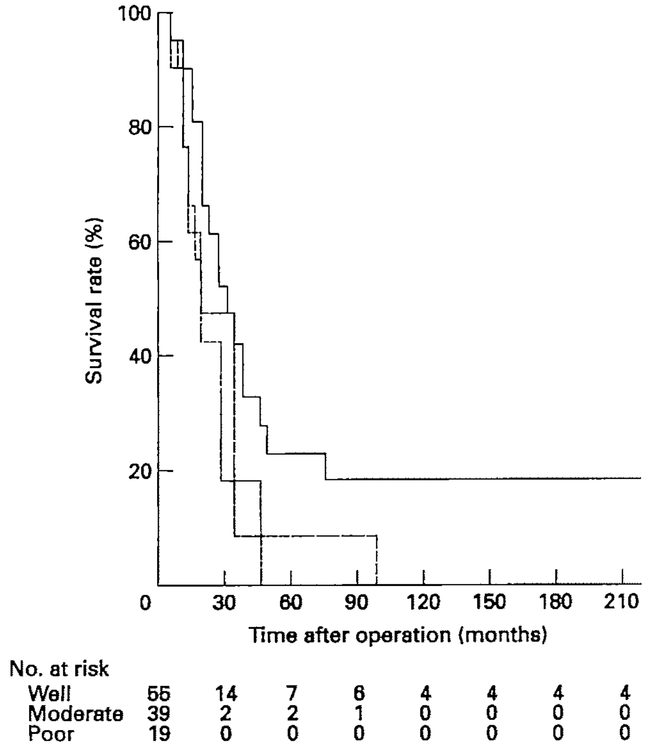

Fig. 2 Actuarial survival rate according to degree of tumour differentiation: well (——), moderately (– – –) and poorly (------) differentiated tumours. $P = 0{\cdot}002$ (Wilcoxon test)

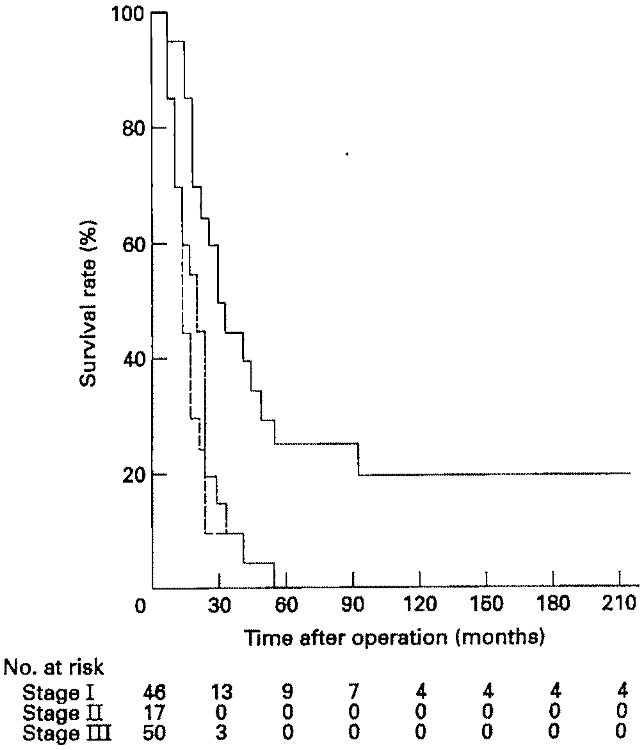

Fig. 3 Actuarial survival rate according to the Union Internacional Contra la Cancrum classification: stage I (——), stage II (– – –) and stage III (------). $P = 0{\cdot}0001$ (Wilcoxon test)

Table 4 Resectability, operative mortality and 5-year survival rates, and number of 5-year survivors, after pancreatic resection in recently published series

Reference	Year	No. of resections	Mortality rate (%)	5-year actuarial survival rate (%)	No. of 5-year survivors
Trede *et al.*[8]	1990	133 (—)	2	24	11 (8)
Manabe *et al.*[11]	1990	74 (—)	8	14	5 (7)
Griffin *et al.*[12]	1990	36 (—)	—	12	4 (11)
Nagakawa *et al.*[13]	1991	49 (36)	14	26	7 (14)
Andren-Sandberg *et al.*[14]	1991	128 (17)	20	—	8 of 101 (8)*
Gall *et al.*[15]	1991	138 (24)	6	11	—
Cameron *et al.*[9]	1991	89 (—)	9	21	—
Sener *et al.*[16]	1991	278 (12)	8	14*	—
Roder *et al.*[17]	1992	53 (—)	2	6	1 (2)
Tannapfel *et al.*[18]	1992	81 (30)	6	13	—
Bakkevold and Kambestad[19]	1993	84 (19)	11	1	1 (1)
Klinkenbijl *et al.*[20]	1993	63 (28)	8	11	6 (10)
Geer and Brennan[21]	1993	146 (18)	5	24	10 (7)
Launois *et al.*[22]	1993	47 (—)	13	8	1 (2)
Willett *et al.*[23]	1993	72 (—)	6	13	—
Sellner and Machacek[24]	1993	49 (24)	—	0	0 (0)
Baumel *et al.*[25]	1994	787 (21)	10	12	15 (2)
Wade *et al.*[26]	1994	288 (23)	8	8	6 (2)
Takahashi *et al.*[27]	1994	137 (57)	14	14	8 (6)
Tsao *et al.*[28]	1994	27 (—)	4	7	—
Allema *et al.*[29]	1994	68 (—)	—	0	0 (0)
Andersen *et al.*[30]	1994	61 (—)	—	13	2 (3)
Total		2888 (20)	9	12	77 (4)
Present series		113 (21)	15	12	9 (8)

Values in parentheses are percentages. *At 3 years significantly influenced by preoperative diabetes ($P = 0{\cdot}001$), age greater than 70 years ($P = 0{\cdot}03$), vascular resection ($P = 0{\cdot}02$), radicality of operation ($P = 0{\cdot}01$), tumour differentiation ($P = 0{\cdot}002$) (*Fig. 2*), lymph node status ($P = 0{\cdot}001$), tumour size ($P = 0{\cdot}008$), perineural infiltration ($P = 0{\cdot}01$) and pathological tumour staging ($P = 0{\cdot}0001$). Multivariate analysis showed that stage ($P = 0{\cdot}0008$), diabetes ($P = 0{\cdot}003$), age ($P = 0{\cdot}01$) and tumour grade ($P = 0{\cdot}03$) were significant independent determinants of long-term survival.

Patients with a stage I tumour had 1-, 3- and 5-year survival rates of 92, 45 and 26 per cent; the values for stage II and III tumours were 77, 8, 0 per cent and 69, 5 and 0 per cent respectively ($P = 0{\cdot}0001$) (*Fig. 3*). Nine patients had radical (R_0) resection for small (2 cm or less), node-negative (T_{1a}, N_0) and well differentiated tumours; excluding hospital mortality (three patients), four of these patients were alive at 5 years.

Cumulative survival did not differ between the two periods: 1-, 3- and 5-year survival rates were 70, 20 and 14 per cent for the first period (1970–1981) and 75, 16 and 11 per cent for the second (1982–1992).

Finally, nine of the 89 patients operated on more than 5 years ago survived for more than 5 years after operation, with a crude 5-year survival rate of 10 per cent. Seven patients are still alive and disease-free at 6–18 years after resection (three after distal pancreatectomy, two after total pancreatectomy and two after pancreaticoduodenectomy), while two died from recurrent disease 7 and 8 years after operation.

Discussion

The resectability and mortality rates achieved in the surgical treatment of pancreatic adenocarcinoma are similar to the cumulative experiences reported recently in the English literature (*Table 4*). Hospital mortality rate after pancreatic resection decreased in the present series, from more than 20 per cent in the earlier period to less than 5 per cent in the later period. The operative mortality rate has been dramatically reduced in all centres with wide experience of pancreatic surgery[6,7], and some authors[8,31] have reported a large number of pancreatic resections without a death. In the authors' opinion this is the major progress registered in recent years in the surgical treatment of pancreatic carcinoma.

Improved survival after resection for pancreatic cancer has also been reported. In 1990 the Japanese Pancreatic Cancer Registry reported an overall survival rate at 3 and 5 years of 22·2 and 16·5 per cent, respectively[32]. Values for 5-year survival of 24 and 21 per cent have been reported by Trede *et al.*[8] and Cameron *et al.*[9] respectively. Furthermore, patients with a stage I tumour, according to the Japanese cancer staging system, had a 5-year survival rate of 30·3 per cent[33], while those without lymph node involvement had an impressive actuarial 5-year survival rate of 35 per cent[8] and 57 per cent[9].

However, it is difficult to compare the Japanese staging system and the classification used in Western countries (American Joint Committee on Cancer or UICC), and the selection of patients undergoing resection may explain the results of some surgeons[8,9]. On the other hand, a change in the biological behaviour of pancreatic carcinoma has been suggested[9]. Unfortunately, the present authors have not experienced similar results, and the data collected from the recent published series[8,9,11–30] (*Table 4*) do not show optimistic results. Among 2888 resections for pancreatic cancer, collected from 1990 to 1994, the resectability rate was quite variable (ranging from 12 to 57 per cent) as a result of different criteria for selection of patients for surgical treatment. The mean actuarial 5-year survival rate was 12 (range 0–26) per cent; two groups[14,16] limited their observation to 3 years, reporting an actuarial 3-year survival rate of 14 per cent and eight (8 per cent) of 101 3-year survivors respectively. Many authors reported the number of 5-year survivors after resection, that is the actual 5-year survival rate. In 15 series, representing 2075 resectional procedures, 77 patients (4 per cent) survived for 5 years. These values are similar to those reported by Gudjonsson[5] in 1987: in his 50-year review of pancreatic cancer surgery, 145 5-year survivors were collected among 4100 patients undergoing resection (4 per cent).

In the present series the overall 5-year survival rate was 12 per cent, well in agreement with the average survival rate of patients who undergo resection for pancreatic cancer in Western countries. Survival was not substantially modified in the last 11 years. If the prognostic parameters affecting long-term survival are considered, the type of surgical procedure did not influence 5-year survival. In fact, in the authors' experience, prognosis was not affected by extension of the pancreatic resection (total or subtotal pancreaticoduodenectomy); on the contrary, a more conservative procedure, such as pylorus-preserving pancreatectomy, achieved the same results as standard resection. Although the present experience with total pancreatectomy and pylorus-preserving pancreatectomy is limited, these findings are confirmed by other reports[34,35]. Long-term results after total pancreatectomy are disappointing because of the lack of improvement in survival, with a considerable morbidity rate[34]. Similarly, extended pancreaticoduodenal resection as described by Fortner[36] has shown no improvement in long-term survival, recording a median survival of 15 months with no survivors at 5 years.

Subtotal pancreaticoduodenectomy has been advocated by Gall[37] as an alternative procedure to total pancreatectomy for the surgical treatment of pancreatic carcinoma to avoid postoperative diabetes. This technique, which the authors have performed since 1982, gave no improvement in long-term survival compared with standard Whipple resection. The extended subtotal duodenopancreatectomy (i.e. enlarged lymph node dissection with resection of peripancreatic tissue) has been emphasized recently by Japanese authors[38,39], who showed an impressive significant prolongation of the survival time in contrast with that in patients treated by less extensive lymph node dissection. A major criticism of the above reports is a lack of adequate randomized controls, since a retrospective historical analysis was performed. A significantly improved 3-year survival rate in patients with pancreatic cancer who underwent radical lymphadenectomy has been reported by the only prospective controlled study published so far[40]; however, the number of patients included was small and further prospective validations are necessary for definitive conclusions to be drawn.

Survival in the present series was influenced by patient characteristics and the biology of the tumour, rather than by the operative procedures. Age of 70 years or more, diabetes, high tumour grade and pathological stage II–III were independent predictors of unfavourable survival. The importance of tumour stage in predicting long-term outcome of patients with malignancy is obvious. Patients with stage I disease had an actuarial 5-year survival rate of 26 per cent, which was similar to the optimistic results reported by other authors[8,9]. Furthermore, if patients with more favourable prognostic parameters are considered (i.e. T_{1a}, N_0, G_1, R_0-resected tumours), 60 per cent of these highly selected patients survive for 5 years. In the authors' opinion, this is the best result that can be achieved by surgical treatment alone in pancreatic cancer. However, stage I constitutes less than half of patients with resected pancreatic cancer and only a small proportion survive longer than 5 years. Actuarial survival does not mean the real number of 5-year survivors; that value is rarely reported and, according to Gudjonsson[5], is presumed to be extremely low. In the authors' experience only nine of 89 patients resected for cancer of the pancreas up to 1989 survived for more than 5 years after surgery.

In conclusion, despite the fact that surgical resection provides the only chance for long-term survival for patients with pancreatic cancer, prognosis does not seem to be related to the type of surgical procedure. Those who survive for 5 years still account for a small number of patients with pancreatic cancer resected for cure, and there has been no real evidence of improved survival in the last decade. These conclusions are supported by the recent report of the Mayo Clinic experience[41], analysing data collected from 1981 to 1991 with 174 resections for pancreatic cancer (overall 5-year survival rate 6·8 per cent). The authors concluded that 'although mortality rates after pancreatic resection have declined, long-term survival remains dismal, and favorable survival rates might therefore be explained as the result of strict and better preoperative selection'.

In the authors' opinion, apart from extended lymphadenectomy, which needs further evaluation, surgery in the near future is not expected substantially to improve the survival rate of the patients with pancreatic carcinoma. Validation of adjuvant therapies is now mandatory to ameliorate the surgical results.

Acknowledgements

This study was supported by a grant from the Italian National Research Council (CNR), contract no. 94.01179.PF39.

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Case report

Spontaneous splenic rupture: a rare complication of acute pancreatitis

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Splenic rupture is a rare complication of acute pancreatitis. Since 1945, only seven cases have been reported after an episode of acute pancreatitis. This report concerns a patient who developed a ruptured spleen as a complication of acute pancreatitis.

Case report

A 52-year-old woman was admitted with a 6-h history of sudden onset of epigastric pain radiating to her back, associated with vomiting. She had no past history of gallstone disease. She reported drinking a bottle of wine per day plus heavy drinking on a recent holiday. On examination, she was afebrile with a pulse rate of 92 per min, blood pressure of 110/60 mmHg and respiratory rate of 20 per min. Examination of her abdomen revealed epigastric tenderness only. Initial investigations showed an amylase concentration of 1932 units/l, white cell count of $12{\cdot}4 \times 10^9$/l, haematocrit of 41 per cent, random serum glucose level of 9·3 mmol/l, serum lactate dehydrogenase concentration of 261 units/l and an aspartate transaminase level of 10 units/l. Initial chest and abdominal radiography, urea and electrolyte concentrations were all normal.

The diagnosis was alcohol-induced pancreatitis with a Ranson score of zero at presentation[1], and the patient was managed conservatively. After 2 days she developed ascites on ultrasonography, with a fall in haematocrit to 35 per cent (greater than 10 per cent drop) and in calcium concentration to 1·92 mmol/l (Ranson score = 2 at 48 h). At 72 h the patient developed bilateral pleural effusions and respiratory failure (arterial partial pressure of oxygen 7·23 kPa). She was commenced on continuous positive airway pressure ventilation and total parenteral nutrition. Computed tomography (CT) of the abdomen at 48 h showed an oedematous pancreas with ascites, a normal spleen and normal common bile duct.

One week later the patient suddenly developed signs of hypovolaemic shock, with pain in the left upper quadrant of the abdomen. Emergency laparotomy revealed a haemoperitoneum due to ruptured spleen and an oedematous pancreas, with no gallstones. Splenectomy was performed, and 50 g splenic tissue (one-third of the total weight) was macerated and reimplanted in the greater omentum. Ten days later, repeat abdominal CT showed a necrotic pancreas with a large cyst in the tail. Ultrasonographically guided aspiration of the pancreatic collection produced 10 ml necrotic material, which was sterile on culture. Histology of the spleen showed surface capsular disruption and laceration with haemorrhage but an otherwise normal spleen. There was no histological evidence of haemopoietic disease, splenic vein thrombosis, or presence of ectopic intrasplenic pancreatic tissue.

The patient remained pyrexial and required further laparotomy at day 24. Pancreatic necrosectomy was performed, together with cholecystectomy, tube gastrostomy and tube jejunostomy, and three drains were left in the pancreatic bed for postoperative irrigation with saline. Peroperative cholangiography was normal. After operation the patient was given antipneumococcal vaccine and penicillin, and was discharged home at 5 weeks. She remains off alcohol and pain-free at 6 months, with a normal blood sugar level and bowel habit.

Discussion

Several mechanisms have been proposed to explain the pathogenesis of splenic rupture in pancreatitis, including splenic vein thrombosis[2], perisplenic adhesions[3], pancreatic pseudocyst erosion into the spleen[4] and acute inflammation of ectopic intrasplenic pancreatic tissue[5]. Neither splenic vein thrombosis nor ectopic intrasplenic pancreatic tissue was present on histological examination in this case. Moreover, no pancreatic pseudocyst or perisplenic adhesions were seen either on the CT scan or at laparotomy.

Most reports in the literature are of splenic rupture secondary to chronic pancreatitis; however, this patient had no previous history of pancreatitis. Spontaneous splenic rupture is a very rare complication of acute pancreatitis, and its cause is unclear.

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Paper accepted 29 September 1995

British Journal of Surgery 1996, 83, 633–636

Immune function early in acute pancreatitis

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Circulating lymphocyte numbers and activation together with granulocyte function were measured in 20 patients in the early stages of an attack of acute pancreatitis and in 20 healthy controls. Circulating lymphocytes, T lymphocytes, and CD4 and CD8 T lymphocyte subsets were decreased in both mild pancreatitis (67–80 per cent of controls) and severe pancreatitis (22–40 per cent of controls). CD4:CD8 ratios were unchanged and median (interquartile range) interleukin 2 receptor expression was increased from less than 1 per cent in controls to 14(6) per cent in severe pancreatitis, suggesting lymphocyte activation. Median granulocyte chemiluminescence was increased to 293 per cent of controls in severe pancreatitis and random motility was reduced to 77 per cent of controls, indicating increased metabolic activity. Complement-mediated antibody-independent opsonization and chemotaxis toward endotoxin were normal. Immune function is not reduced early in acute pancreatitis. Granulocyte hyperactivity may be important in the development of multiple organ failure.

Pancreatic infection is a leading cause of morbidity and mortality in acute pancreatitis[1,2]. Pathogens may arise from several sources, including the colon and biliary tract, and they reach the pancreas by different routes[3,4]. However, contamination of the healthy gland does not lead to infection[5]. Infection may develop as a complication in patients with acute pancreatitis. Understanding of the factors responsible for this increased risk may lead to improved treatment.

The risk of infection is proportional to the severity of pancreatitis and the extent of pancreatic necrosis[5–10]. Several lines of evidence, however, suggest that host immune function may also be important. Reduced delayed hypersensitivity skin test response to recall antigens (anergy) early in acute pancreatitis is associated with increased risk of sepsis and death[11]. Circulating T helper cell numbers are decreased early in acute pancreatitis[12], a finding that may be associated with immune deficiency. The rate of clearance of bacteria and proteases is decreased[13–15], suggesting impaired reticuloendothelial system function. It was hypothesized that immune function is reduced in acute pancreatitis. The aim of this study was to investigate immune function early in acute pancreatitis. Changes within the first 48 h of admission to hospital were measured before the effects of infection, starvation and multiple organ failure became important[16,17].

Patients and methods

Twenty consecutive patients with acute pancreatitis and 20 healthy controls (blood transfusion donors aged 18–65 years) were enrolled and informed consent was obtained. Severity was assessed by the Atlanta criteria[18] although patients with clinically uncomplicated attacks did not undergo computed tomography. C-reactive protein (CRP) levels were measured on an AXON analyser (Bayer, Basingstoke, UK). The development of extraintestinal organ failure was defined according to established criteria[19]. Venous blood samples were taken within 48 h of onset of acute pancreatitis and analysed immediately. All samples were drawn between 08.00 and 10.00 hours to exclude variability due to diurnal rhythm[20]. Lymphocytes were separated from ethylenediamine tetra-acetic acid-anticoagulated venous blood by density-gradient centrifugation[12]. The lymphocyte surface antigens CD3 (T lymphocytes), CD4 (helper–inducer T lymphocytes), CD8 (suppressor–cytotoxic T lymphocytes), CD19 (B lymphocytes) and expression of CD25 (interleukin (IL) 2 receptor) were measured by indirect immunofluorescence. Granulocytes were separated from heparinized blood avoiding procedures likely to cause activation[21]. The following functions were determined: granulocyte chemiluminescence, complement-mediated antibody-independent opsonization, granulocyte chemotaxis toward endotoxin, and random migration. All assays were completed with 6 h of sampling.

Indirect immunofluorescence

Lymphocytes suspended in phosphate-buffered saline (PBS)–bovine serum albumin at 2×10^6 cells/ml were incubated with 5 μl antibody (Dako, High Wycombe, UK) at 4°C for 15 min. Cells were then washed with 1 per cent PBS–paraformaldehyde before being mixed with 5 μl fluoroscein isothiocyanate–rabbit anti-mouse F $(ab')_2$ (Dako) and incubated at 4°C for 15 min. Samples were washed again in 1 per cent PBS–paraformaldehyde, the supernatant was discarded and cells were analysed on a FACScan (Beckton Dickinson, Oxford, UK) using the LYSYS II program. Absolute numbers of lymphocytes were calculated as:

$$\text{Absolute lymphocyte count} = \text{total lymphocyte count} \times (\text{percentage of CD marker}/100)$$

Internal quality control was performed before each count using Immunocheck beads (Coulter, Luton, UK) and Cytotrol, a freeze-dried preparation of normal lymphocytes (Coulter).

Granulocyte metabolic activity

Granulocyte metabolic activity was measured by luminol (5-amino-2,3-dihydrophthalazine-1,4-dione; BDH Chemicals, Poole, UK)-enhanced chemiluminescence and compared with a control assay performed simultaneously[22,23]. This is a biological assay that gives a measure of granulocyte phagocytic and bactericidal metabolic activity compared with controls[22–25]. Granulocyte chemiluminescence was initiated by the addition of preopsonized zymosan. The reagents (100 μl PBS containing 5×10^6 granulocytes/ml, 200 μl zymosan suspension (12 mg/ml) and 700 μl 10^{-4} mmol/l luminol), equilibrated to 37°C in a water bath, were mixed and luminometer readings (mV) were taken at 1-min intervals for 10 min. The area under each curve was measured and data were expressed as a percentage of controls. Antibody-independent opsonization was assessed by comparing

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Presented to the British Society of Gastroenterologists in Edinburgh, UK, September 1994 and published in abstract form as *Gut* 1994; 35: S67 and S35
Paper accepted 1 October 1995

the chemiluminescence of control granulocytes stimulated by patient plasma-opsonized zymosan with that of granulocytes stimulated by control plasma-opsonized zymosan.

Granulocyte motility

Granulocytes demonstrate both unstimulated random migration and directional migration in response to a chemoattractant gradient[26]. Motility was measured by a modification of the Boyden chamber technique[27]. Hank's balanced salt solution with or without chemotactic agent (endotoxin 1·5 mg/ml) was placed in wells of a granulocyte migration plate and covered with a 13-mm diameter 3-μm pore filter. The granulocyte suspension was placed on the filter and incubated at 37°C for 90 min. The following combinations were set up in duplicate: control or patient cells with chemoattractant, and control or patient cells with no chemoattractant. Filters were removed and soaked in propan-2-ol; migration was then assessed by the leading-front method. Results were expressed as a percentage of the movement of patient cells compared with controls.

Statistical analysis

All data were expressed as median(interquartile range) and compared by the Mann–Whitney *U* test. Correlation coefficients were calculated by linear regression.

Results

Twenty healthy controls, and 14 patients with mild and six with severe acute pancreatitis were studied. There was no difference in the age of patients with mild or severe pancreatitis (55(22) *versus* 61(30) years, $P = 0·3$) or in the sex ratio (male:female ratio 1:1 in both mild and severe acute pancreatitis). The aetiologies were also similar between groups. Acute Physiology And Chronic Health Evaluation II[28] scores were higher in patients with severe pancreatitis at 15(5) than in those with mild pancreatitis at 6(5) ($P = 0·01$). Organ failure was also more frequent in severe disease (2(3) *versus* 0(0) respectively, $P = 0·01$). The CRP level was also increased in severe pancreatitis at 144(55) mg/l compared with 41(95) mg/l in mild pancreatitis ($P = 0·05$).

Two of six patients with severe pancreatitis died (10 per cent mortality rate overall). One patient, aged 88 years, died within 48 h from multiple organ failure; the other, aged 65 years, died from multiple organ failure after necrosectomy for infected pancreatic necrosis. One patient with severe pancreatitis had a pancreatic abscess drained surgically.

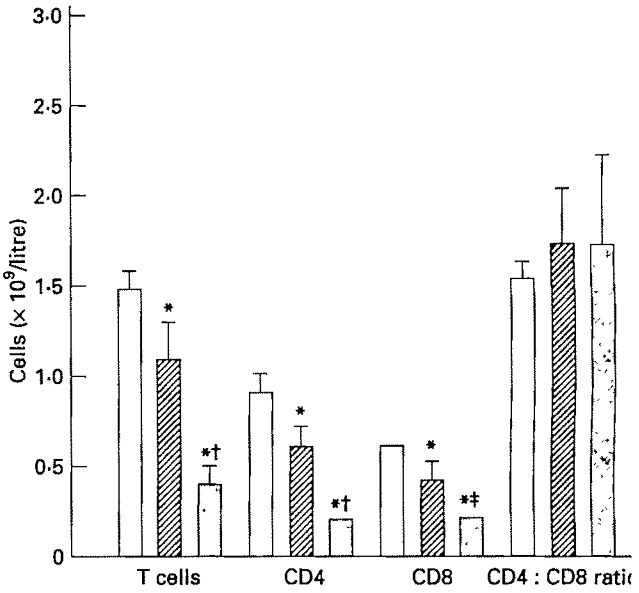

Fig. 2 Effect of acute pancreatitis on T lymphocyte subsets in controls (□), and in mild (▨) and severe (□) acute pancreatitis. Values are median(interquartile range). $^*P < 0·05$ *versus* controls, $†P < 0·02$ *versus* mild acute pancreatitis, $‡P = 0·06$ *versus* mild acute pancreatitis

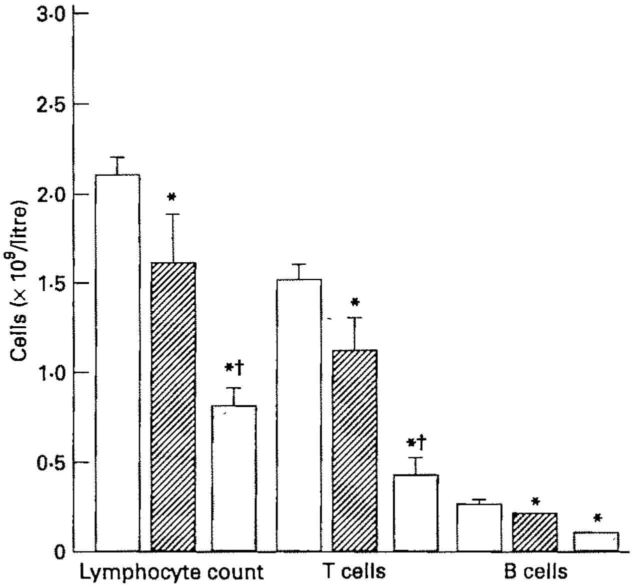

Fig. 1 Changes in circulating lymphocytes in controls (□), and early in mild (▨) and severe (□) acute pancreatitis. Values are median(interquartile range). $^*P < 0·05$ *versus* controls, $†P < 0·02$ *versus* mild acute pancreatitis

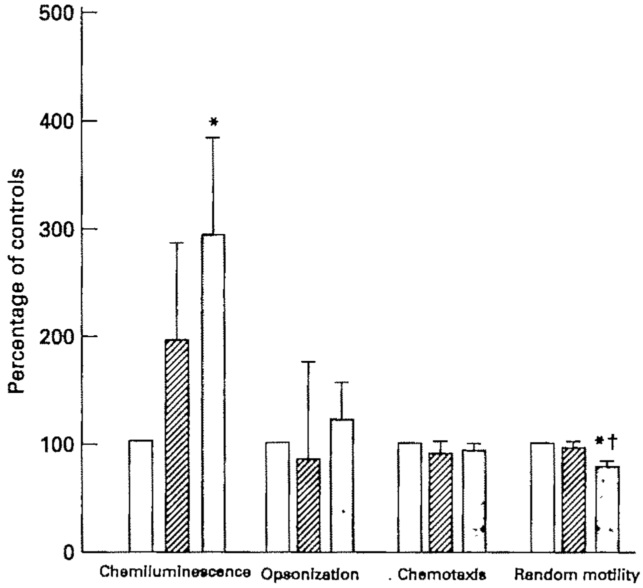

Fig. 3 Changes in granulocyte function in controls (□), and early in acute mild (▨) and severe (□) pancreatitis. Values are median(interquartile range). $^*P < 0·05$ *versus* controls, $†P < 0·05$ *versus* mild acute pancreatitis

Total lymphocyte, and T and B lymphocyte counts were all reduced in both mild and severe acute pancreatitis compared with controls (*Fig. 1*). T cell subsets CD4 and CD8 were reduced in both mild and severe acute pancreatitis compared with controls (*Fig. 2*). There was no change, however, in CD4:CD8 T lymphocyte ratio. CD25 expression was increased compared with controls in both mild (6(2) per cent) and severe (14(6) per cent) acute pancreatitis ($P < 0{\cdot}01$). CRP levels were inversely proportional to total lymphocyte count ($r = 0{\cdot}7$), T lymphocytes ($r = 0{\cdot}7$), CD4 T lymphocytes ($r = 0{\cdot}7$) and CD8 T lymphocytes ($r = 0{\cdot}5$) (all $P < 0{\cdot}05$), but not to CD4:CD8 ratio ($r = 0{\cdot}1$).

In acute pancreatitis, and particularly in severe disease, granulocyte chemiluminescence was increased suggesting that granulocytes were metabolically hyperactive (*Fig. 3*). Random motility was reduced in severe pancreatitis. Antibody-independent opsonization and granulocyte chemotaxis were unchanged (*Fig. 3*).

Discussion

Circulating lymphocytes, T lymphocytes, and CD4 and CD8 T lymphocyte subsets were all decreased early in acute pancreatitis. Changes were inversely proportional to the severity of pancreatitis and to the acute-phase response as measured by the level of CRP. The observation that circulating CD4 helper T lymphocytes were depleted confirmed a previous report[12]. It is unlikely, however, that this constituted impaired host immunity[12] because the CD4:CD8 ratio remained unchanged. In immunosuppressed patients CD4 lymphocytes are selectively depleted and the CD4:CD8 ratio is decreased[20,29]. In addition, IL-2 receptor expression in acute pancreatitis was increased. In immunosuppressed patients this is reduced[29–31]. Increased IL-2 receptor (CD25) expression showed that lymphocytes were activated and undergoing clonal proliferation, a normal response to processed antigen[32].

Circulating lymphocytes are a small fraction of the total population. Lymphocytes continuously recirculate from the blood pool to the lymph nodes, Peyer's patches, spleen and peripheral vessels. Normally, lymphocytes returning via efferent lymphatics maintain a stable blood pool[20,33]. Decreased efflux occurs in response to antigen stimulation[33]. Redistribution of lymphocytes from the blood pool may therefore account for the fall rather than impaired immune function. Further studies are needed to investigate lymphocyte kinetics and function.

Increased chemiluminescence and reduced random motility showed that granulocytes were metabolically hyperactive. Granulocyte activation is therefore an early event in acute pancreatitis. In support of this finding is the observation that the activity of serum granulocyte elastase, which is released when such cells degranulate, is raised early in acute pancreatitis[12,34,45]. Granulocyte activity is increased[12,35–41] by activated complement, endotoxin and IL-6. In acute pancreatitis, serum levels of these inflammatory mediators are raised[12,42–44] and the present study demonstrated that complement-mediated opsonization of zymosan and chemotaxis toward endotoxin were both normal.

Granulocyte activation is a normal response to inflammation and is likely to enhance host resistance to infection. Excessive or uncontrolled activation may, however, cause multiple organ failure[17,45–48]. Systemic release of toxic mediators (cytokines, kinins, oxygen radicals, eicosanoids, platelet-activating factor and nitric oxide) from activated granulocytes can lead to shock, multiple organ failure and death[37,45,47,49,50], and neutrophil depletion protects against lung injury in animal models of acute pancreatitis[51,52].

This study investigated two components of the immune system: lymphocytes and granulocytes. Mononuclear phagocytic cells are a third important component. Previous studies showed a decreased rate of clearance of bacteria and proteases, suggesting reduced mononuclear phagocytic function[13–15]. However, phagocytic cells have a finite capacity to remove particles, including bacteria and protease–antiprotease complexes. It is likely, therefore, that the systemic release of large amounts of pancreatic proteases during acute pancreatitis saturates phagocytic capacity, thus reducing the rate of clearance of infused bacteria or proteases[14]. This does not imply impaired function but is caused instead by host capacity being overwhelmed.

In conclusion, immune function is not reduced early in acute pancreatitis. However, granulocyte hyperactivity occurs early and may be important in the development of multiple organ failure.

Acknowledgements

The authors are grateful for the assistance of Dr T. B. Wallington and the staff of the Regional Immunology Service, Bristol.

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British Journal of Surgery 1996, 83, 637–641

Donor arterial variations in liver transplantation: management and outcome of 527 consecutive grafts

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The impact of donor arterial variations and their management was investigated retrospectively in 527 consecutive allografts. Anomalous arteries were found in 161 grafts (30·6 per cent). There was no significant difference in the overall incidence of arterial complications between grafts with normal (3·6 per cent) and abnormal (5·6 per cent) anatomy. However, there was a higher incidence of arterial complications in transplants requiring multiple arterial anastomoses ($P = 0·02$), or anastomosis of donor vessels to recipient aorta with ($P = 0·0003$) or without ($P = 0·04$) an interposition graft for arterial reconstruction. The incidence of biliary complications was similar in grafts with a normal (18·8 per cent) or anomalous (18·0 per cent) arterial supply. Anomalies of hepatic arterial anatomy occur in one-third of all livers and do not compromise graft outcome unless multiple anastomoses or direct anastomosis to the recipient aorta are required for arterial reconstruction.

Hepatic arterial anomalies occur in 12–49 per cent of all livers[1–7]. Recognition and appropriate reconstruction of such variants are essential in liver transplantation since the absence of an adequate hepatic arterial supply usually results in graft loss due to ischaemic biliary and/or parenchymal complications[8,9]. While some reports indicate that arterial anomalies do not affect the incidence of arterial and biliary complications[1,4,8], others have found that they increase the incidence of arterial complications[9]. Most of these studies were based on a relatively small number of grafts and none has analysed the effect of the techniques of management of these anomalies on the post-transplant complications. The optimal management of anomalies in reduced size grafts is also unclear. This study analyses the effect of anomalous donor hepatic arterial supply and its management on postoperative arterial and biliary complications, as well as outcome following transplantation with whole or reduced liver grafts, in a large consecutive series.

Methods

A total of 529 liver transplants was carried out between January 1988 and January 1994. There were two intraoperative deaths. Operative records of the remaining 527 grafts were reviewed for the details of donor arterial anatomy, methods of biliary and arterial reconstruction and the techniques used to manage arterial anomalies. The effect of these parameters on the postoperative incidence of the following complications was then analysed.

1. Biliary complications, defined as a leak or stricture requiring definitive endoscopic or surgical intervention.
2. Hepatic artery complications, comprising hepatic artery thrombosis (including stenosis) and/or pseudoaneurysm leading to graft loss (death or retransplant) or requiring arterial reconstruction. The diagnosis was confirmed on arteriography and/or at operation in all cases.
3. Non-thrombotic hepatic infarction (NTHI), defined as histologically documented infarction without major vascular thrombosis in a graft which functioned initially but subsequently failed without any apparent cause[10].
4. Chronic rejection.
5. Graft loss.

The follow-up period ranged from 1 to 7 years.

Donor operation

All grafts were perfused in standard fashion with Marshall's solution via the aorta and University of Wisconsin (UW) solution via the portal vein, harvested using standard techniques and, after further flushing the hepatic artery with UW solution, preserved in UW solution at 4°C.

Recipient operation

Some 467 of the transplants were whole and there were 60 reduced grafts including 39 left lateral segments, 11 left lobes, eight right trisegments and two right lobes.

Arterial reconstruction. In most cases, the main anastomosis was between either the donor hepatic artery/coeliac artery branch patch/Carrel patch and the recipient hepatic artery branch patch (method 1a, $n = 320$), or directly between the donor hepatic artery/coeliac artery and the recipient hepatic artery (method 1b, $n = 178$). In cases where the recipient hepatic artery had inadequate flow or calibre, the donor hepatic artery/coeliac artery was anastomosed to the recipient aorta either directly (method 2, $n = 11$) or with an interposition graft (method 3, $n = 18$). The anastomosis to the aorta was infrarenal in 12 cases (all with an interposition graft) and supracoeliac in 17 (11 direct and six with interposition grafts).

Any aberrant left hepatic artery not arising from the coeliac artery, or if accidentally divided, was anastomosed to one of the branches of the coeliac artery. Aberrant right hepatic arteries were managed either by using the superior mesenteric artery (SMA) bearing the aberrant artery as a conduit between the donor and the recipient coeliac artery/hepatic artery or by anastomosing the aberrant right hepatic artery or the SMA to the splenic artery stump on the coeliac artery (*Fig. 1*; methods 4 and 5 respectively). The term 'aberrant' has been used to describe the anomalous arteries since it may not always be possible to determine whether an abnormal artery is an accessory to or replacing the artery present normally. Where there were anomalous hepatic arteries in the recipient (e.g. aberrant right

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hepatic artery), the artery with the widest calibre and the best lie was used for construction of the arterial anastomosis.

More than one anastomosis was required either when more than one donor artery was not from a common aortic source (e.g. main artery from coeliac artery and aberrant right hepatic artery from SMA) or when interposition arterial grafts were used (method 3).

Vascular anastomoses were performed in the order suprahepatic vena cava, infrahepatic vena cava, portal vein and hepatic artery; the liver was perfused initially with portal blood and then with arterial blood (sequential perfusion). However, in cases where the supracoeliac aorta was used, the arterial anastomosis was carried out first and, after completion of other vascular anastomoses, the liver was perfused simultaneously with arterial and portal blood.

Biliary reconstruction. End-to-end anastomosis between the donor and recipient ducts or end-to-side anastomosis of the donor duct to a Roux-en-Y loop of the recipient jejunum was performed.

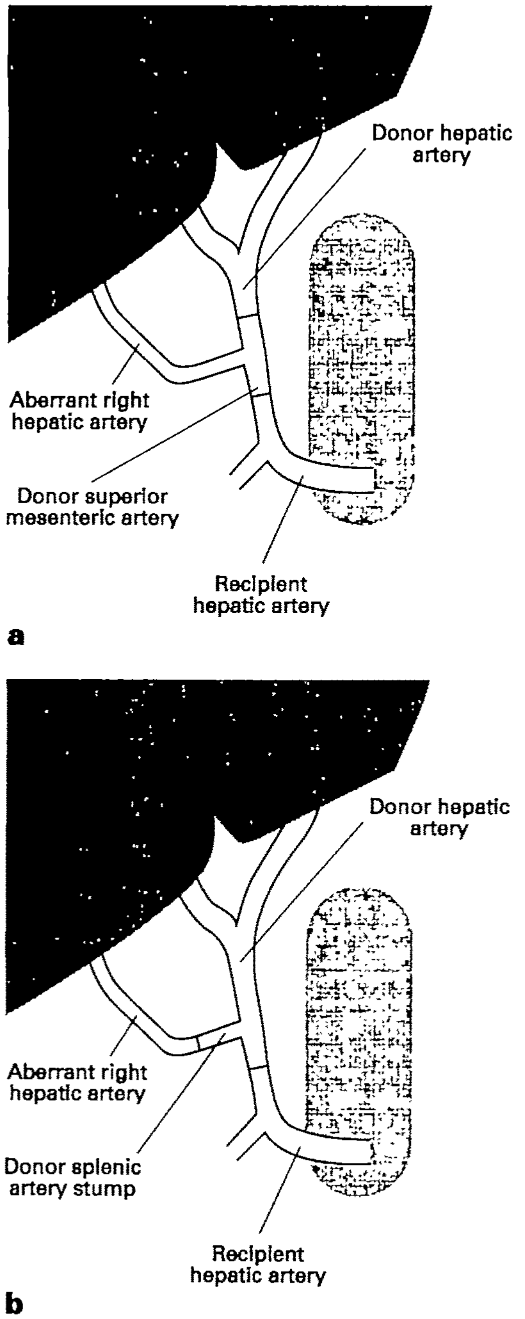
Donor hepatic artery
Aberrant right hepatic artery
Donor superior mesenteric artery
Recipient hepatic artery
a
Donor hepatic artery
Aberrant right hepatic artery
Donor splenic artery stump
Recipient hepatic artery
b

Fig. 1 Aberrant right hepatic artery was managed either **a** using the superior mesenteric artery bearing the aberrant artery as a conduit between the donor and the recipient coeliac artery/hepatic artery or **b** anastomosing the aberrant right hepatic artery or the superior mesenteric artery to the donor splenic artery stump

Immunosuppression

Recipients of 481 of the grafts received triple immunosuppression with cyclosporin, azathioprine and prednisolone, and 46 received FK506-based immunosuppression as a part of two clinical trials.

Statistical methods

Fisher's exact test and χ^2 test with Yates' correction for small numbers were used. Survival curves were derived using the Kaplan–Meier method and differences in survival were computed using the log rank test. A P value less than 0·05 was considered statistically significant.

Results

Donor arterial anatomy

Arterial anatomy was normal in 366 grafts and anomalous arteries were found in 161 (30·6 per cent) of the donor livers. These consisted of aberrant left hepatic arteries in 75 (14·2 per cent), aberrant right hepatic arteries in 44 (8·3 per cent), main hepatic artery arising from the SMA in 12 (2·3 per cent), and aberrant left hepatic artery and aberrant right hepatic artery along with the main hepatic artery in nine (1·7 per cent). Eleven other rare variants were encountered (*Table 1*).

The incidence of hepatic arterial anomalies was no

Table 1 Types of hepatic arterial anatomy in 527 grafts

	n
HA from CA (normal)	366 (69)
Common variants	
HA from CA, ALHA from LGA	75 (14·3)
HA from CA, ARHA from SMA	44 (8·3)
HA from SMA	12 (2·3)
HA from CA, ALHA from LGA, ARHA from SMA	9 (1·7)
Rare variants	
ALHA from LGA, ARHA from SMA; no HA	4 (0·8)
ALHA from supracoeliac aorta, HA from CA	3 (0·6)
HA, ALHA and ARHA from CA	3 (0·6)
ARHA from CA, HA from CA*	2 (0·4)
ALHA and HA from CA, ARHA from SMA*	2 (0·4)
ALHA from LGA arising from aorta, HA from CA	2 (0·4)
ALHA from GDA, HA from CA, ARHA from SMA*	1 (0·2)
HA from aorta	1 (0·2)
ARHA and HA from SMA, ALHA from LGA*	1 (0·2)
ALHA and HA from CA	1 (0·2)
Dual origin of single HA from SMA and CA	1 (0·2)

Values in parentheses are percentages. *Previously unreported. HA, main or common hepatic artery; CA, coeliac axis; ALHA aberrant left hepatic artery; LGA, left gastric artery; ARHA, aberrant right hepatic artery; SMA, superior mesenteric artery; GDA, gastroduodenal artery greater in donors who died from intracranial haemorrhage due to cerebral aneurysm or arteriovenous malformation than in those dying from other causes (56 of 194 (28·9 per cent) *versus* 105 of 333 (31·5 per cent)).

Hepatic arterial complications

Hepatic arterial complications, namely hepatic artery thrombosis ($n = 19$) and pseudoaneurysm ($n = 3$) developed in 4 per cent ($n = 22$) of all grafts. However, there was no significant difference between their incidence in transplants with a normal (13 of 366 (3·6 per cent)) or anomalous arterial supply (nine of 161 (5·6 per cent)). Similarly, the arterial anatomy did not significantly influence the incidence of hepatic arterial complications when whole and reduced grafts were considered separately. No particular type of anatomical abnormality was associated with a significantly increased incidence of arterial complications (*Table 2*).

However, grafts that required arterial reconstruction with more than one anastomosis had a significantly higher incidence of arterial complications than those with single anastomoses (seven of 72 (10 per cent) *versus* 15 of 455 (3·3 per cent); $P = 0{\cdot}02$). The method of reconstruction was also found to influence the incidence of arterial complications. Overall, arterial complications occurred least commonly with methods 1a and 1b, there being no significant difference between the two (nine of 320 (2·8 per cent) *versus* six of 178 (3·4 per cent)). Method 2 (anastomosis of donor artery to recipient aorta) was associated with significantly more hepatic artery complications than method 1 (two of 11 *versus* 15 of 498; $P = 0{\cdot}04$). The difference between methods 1 and 3 (anastomosis of donor artery to recipient aorta with an interposition graft) was even more striking (15 of 498 *versus* five of 18; $P = 0{\cdot}0003$).

Both techniques of aberrant right hepatic artery revascularization yielded satisfactory results with no significant difference in the arterial complication rate (method 4 two of 34 *versus* method 5 one of 22).

Biliary complications (Table 2)

Overall, there was no significant difference in the incidence of biliary complications between grafts with normal (18·8 per cent) and abnormal (18·0 per cent) arterial anatomy. The findings were similar when whole and reduced grafts, and grafts with duct-to-duct and duct-to-Roux anastomoses were considered separately.

A very high rate of ischaemic biliary and/or parenchymal complications was found in the following instances. In four patients who received left lobes ($n = 2$) or LLS grafts ($n = 2$) the aberrant right hepatic artery was inevitably sacrificed; two of these patients subsequently developed biliary stricture, and one graft was lost because of non-thrombotic infarction. A further four patients who received left lateral segment grafts based only on the aberrant left hepatic artery (with sacrifice of the main hepatic artery) lost their grafts early (non-thrombotic infarction one, primary non-function one, ischaemic biliary complications two).

Non-thrombotic hepatic infarction (Table 2)

The incidence of postoperative NTHI was not significantly different in the groups with normal (5·2 per cent) and anomalous (2·5 per cent) arterial supplies. This difference remained insignificant for whole and reduced grafts

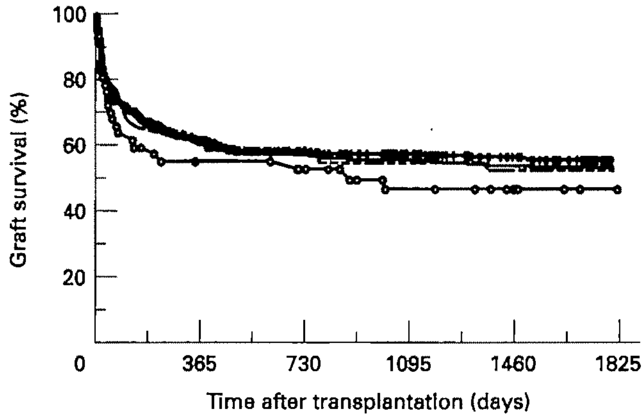

Fig. 2 Five-year actuarial survival of grafts with normal and common variants of hepatic arterial supply. ———, All grafts ($n = 527$); —+—, normal arterial supply ($n = 366$); ——○——, aberrant right hepatic artery ($n = 44$); ----, aberrant left hepatic artery ($n = 75$). The difference in survival between various groups of grafts was not statistically significant (log rank test)

Table 2 Complications in whole and reduced grafts with different variants of hepatic arterial supply

	Arterial supply													
	1		2		3		4		5		6		Total	
	Whole ($n = 328$)	Reduced ($n = 38$)	Whole ($n = 64$)	Reduced ($n = 11$)	Whole ($n = 40$)	Reduced ($n = 4$)	Whole ($n = 11$)	Reduced ($n = 1$)	Whole ($n = 9$)	Reduced ($n = 0$)	Whole ($n = 15$)	Reduced ($n = 6$)	Whole ($n = 467$)	Reduced ($n = 60$)
Arterial complications	10	3	2	1	3	1	0	0	0	0	2	0	17	5
Biliary complications	60	9	12	2	7	2	0	1	2	0	2	1	83	15
NTHI	12	7	2	1	0	1	0	0	0	0	0	0	14	9
Chronic rejection	43	4	13	3	9	1	2	0	2	0	2	2	71	10
Graft loss	133	24	25	9	20	3	4	1	4	0	10	4	198	39

Arterial supply: 1, hepatic artery from coeliac artery; 2, hepatic artery from coeliac artery, aberrant left hepatic artery from left gastric artery (LGA); 3, hepatic artery from coeliac artery, aberrant right hepatic artery from superior mesenteric artery (SMA); 4, hepatic artery from SMA; 5, hepatic artery from coeliac artery, aberrant left hepatic artery from LGA, aberrant right hepatic artery from SMA; 6, other (rare) variants. NTHI, non-thrombotic hepatic infarction considered separately. Similarly, the method of arterial reconstruction was not found to have any bearing on its incidence.

Chronic rejection (Table 2)

The arterial anatomy did not significantly influence the incidence of chronic rejection (47 of 366 *versus* 34 of 161 for grafts with normal and anomalous arterial supply respectively) for whole or reduced grafts.

Graft survival (Fig. 2)

Of 527 grafts, 237 (45·0 per cent) were lost over a follow-up period of 1 to 7 years. Although a higher proportion of grafts with abnormal anatomy was lost, the difference was not statistically significant (157 of 366 (42·9 per cent) *versus* 80 of 161 (49·7 per cent)). The findings were similar when the data were analysed for different arterial arrangements and graft types (*Table 2*).

Discussion

This study has added further to the expanding list of variations in the hepatic arterial supply[2–5,10–14]. The authors could find no previous reports of some of the anomalies (*Table 2*). The donor surgeon can thus expect to find 'normal' hepatic arterial anatomy in only about two-thirds of cases. In the remainder, any combination and number of arteries arising from the coeliac artery, SMA or aorta at that level may be expected. In addition, although not specifically alluded to in this study, abnormal arteries often run tortuous courses in varying relations to the oesophagus, stomach, duodenum, pancreas and the hepatic hilar structures. Although the 'normal pattern' of the arterial supply of hepatic parenchyma and biliary tract is well described[15,16], there is considerable variation in the relative contribution of the normal and abnormal arteries to the parenchyma[2,17] and biliary tree[18] in the presence of anomalies. In addition, the branches of the hepatic artery supplying the liver are essentially end-arteries. Therefore, in the context of a liver transplant, all anomalous vessels, however small, must be preserved and revascularized to avoid ischaemic parenchymal and biliary tract complications.

It seems logical that the incidence of arterial complications should depend on the reconstructive technique rather than the mere presence of anomalous arteries. It is therefore not surprising that, as in some previous reports[1,8], arterial anomalies *per se* did not lead to more arterial complications. However, reconstruction involving multiple anastomoses increased the risk significantly. Since whole or right-sided grafts with aberrant right hepatic arteries ($n = 56$) always required more than one anastomosis, it is conceivable that this anomaly might have emerged as an independent risk factor if a bigger sample of such grafts were available for analysis. Even if this were the case, the increase in risk is unlikely to be high enough to discourage the use of livers with aberrant right hepatic arteries.

The higher risk of arterial thrombosis with an anastomosis to the recipient aorta is likely to have been related to the increased likelihood of kinking, abnormal flow patterns and compression by the adjacent viscera of a long and tortuous donor artery following a non-anatomical course to the aorta. In fact, the presence of two or more anastomoses coupled with the above anatomical factors in cases with an interposition graft to the aorta increased the risk of arterial complications even further.

Non-thrombotic graft infarction is an ill-understood entity and its relationship, if any, with major vessel or microvascular occlusion is not clear. In this study, the presence of arterial anomalies did not affect its incidence.

The overall incidence of biliary complications was not influenced by the presence of arterial anomalies for any graft type or biliary reconstruction technique. However, a high biliary complication rate was encountered in left lobar and left lateral segment grafts where either an aberrant right hepatic artery or the main hepatic artery was sacrificed. This bears out recent anatomical observations in resin casts of cadaveric livers that the main hepatic artery, or aberrant right hepatic artery when present, is the major supraduodenal source of arterial supply to the bile duct[18]. This is especially important in the transplanted liver which is devoid of the usual arterial supply to the biliary tract from the retroportal and retroduodenal arteries[16,18]. These complications might be avoided by constructing a biliary anastomosis high up on the donor duct (at the level of the left duct) in left-sided grafts from livers with an aberrant right hepatic artery, and by resisting the temptation to base a left lateral segment graft on an aberrant left hepatic artery alone. Any arterial contributions from the main or the right hepatic artery to the parenchyma or the biliary tract of the reduced segment, especially in the case of a left lateral segment with an aberrant left hepatic artery, may be preserved by taking care to divide the right arterial branches in the substance of the right half of the liver, i.e. well away and cephalad from the bifurcation.

Despite the ischaemic complications in the few cases cited, the incidence of chronic rejection and graft loss was similar in grafts with normal and anomalous arterial anatomy.

In conclusion, arterial anomalies preserved and managed appropriately do not necessarily compromise graft outcome. While no particular arterial configuration precludes the use of a donor liver as a whole or reduced graft, more arterial complications can be anticipated with complicated arterial reconstructions. Furthermore, the use of a long length of common bile duct in a left segmental or lobar graft with an aberrant right hepatic artery and a left lateral segment supplied solely by an aberrant left hepatic artery, should be avoided.

Acknowledgements

The authors are grateful to Mr Philip Ball and Mr Mike Smith for their help with illustrations and data collection respectively.

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Editor's announcement

Illustrations in colour

The Journal does not contain many illustrations in colour at present, probably because authors are usually requested to make a contribution towards the cost of colour reproduction. This cost is substantial, amounting to approximately £500 per figure at current rates. In association with the publishers, Blackwell Science Ltd, The British Journal of Surgery Society is keen to increase the number of colour illustrations in the Journal. The use of colour is particularly appropriate for operative photographs (whether open operation or laparoscopy), resection specimens and especially photomicrographs. To encourage the submission of suitable illustrations in colour, authors' charges will be waived. Three high-quality prints of each figure should be submitted.

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British Journal of Surgery 1996, 83, 642–643

Antegrade colonic enemas

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Thirteen children aged 6–14 (mean 8) years in whom an antegrade colonic enema procedure was performed were reviewed retrospectively. All presented with refractory constipation or faecal soiling over a 3-year period. Nine of the children had previously undergone pull-through procedures for Hirschsprung's disease or high anorectal malformations. Two were suffering from spina bifida and two from idiopathic functional constipation. The operation was performed through a right iliac fossa incision. A catheterizable conduit was created. The appendix was brought out to the wound edge and made continent by intussuscepting the appendix base into the caecum. When the appendix was absent or unusable, a caecal tube was formed. Five patients suffered minor morbidity, six required a further operative procedure and two eventually required a sigmoid colostomy. However, the eventual outcome of a continent stoma was attained in 11 of the 13 children, all of whom would have been considered for sigmoid colostomy before introduction of the antegrade colonic enema procedure.

Antegrade colonic enemas have been developed as an effective method of treating severe constipation and faecal soiling[1–3]. These conditions are both physically and emotionally devastating, and they significantly affect social life. Various methods of volume enemas have been used in the past, from retrograde continent to antegrade enemas[1,4]. Shandling and Gilmore[4] reported excellent results in patients with spina bifida with the enema continence catheter. However retrograde enemas can be difficult to manage and require assistance in many circumstances, especially in adolescence and adult life. The antegrade colonic enema has been developed to produce a continent appendiceal conduit that can be easily catheterized for self-administration of the enema fluid[1,2]. It is important for good results that both patient and family are motivated, as well as having an understanding of the principles of the procedure[1,5]. This study reviewed the operative procedure and resulting physical morbidity associated with construction of an antegrade colonic enema stoma.

Patients and methods

Children were selected for the procedure on the basis of refractory constipation or faecal soiling, where formation of a colostomy was being considered, due to unacceptable symptoms. Thirteen consecutive antegrade colonic enema procedures carried out during the 3-year period 1991–1993 were reviewed retrospectively. The children were affected by anorectal malformations or Hirschsprung's disease (nine patients), spina bifida (two) or idiopathic functional constipation (two). All had remained symptomatic despite other methods to control the problems.

Three types of operation were used: (1) an intussuscepted appendiceal stump cut across and sutured flush to the lateral margin of the incision; (2) an appendiceal stump formed in the same manner, spliced along the antimesenteric border and sutured in a 'fish-tailed' fashion to a flap of skin to bury the appendiceal mucosa; and (3) when the appendix was absent or unusable, part of the caecum was used to form a tubular structure and this was intussuscepted into the remaining caecum and sutured flush to the skin. In each case the operation was performed under general anaesthesia through a right iliac fossa incision. Standard antibiotic prophylaxis with cefuroxime and metronidazole was used in each case.

The outcome of each operation was a catheterizable stoma in the right iliac fossa. A 10–12-Fr catheter was inserted into the stoma and remained in place for 1 month after operation. At 2 weeks after surgery the daily enema fluid regimen was started using 750–1000 ml polyethyleneglycol 3350 via the catheter. The ideal instillation time was less than 30 min. Tap water (0·5–1 litre) was added to the enema fluid if the polyethylene glycol regimen alone failed, to counter the high osmotic load. If both the above regimens failed, phosphate enemas were introduced to the enema fluid. After 1 month, intermittent catheterization could be used as required (usually on alternate days) to control symptoms. A successful outcome was defined as when the child attained faecal control along with resolution of the presenting symptoms.

Results

This study reviewed complications of the operative procedure and any morbidity resulting from the formation of an antegrade colonic enema stoma over a 3-year period. Thirteen children aged 6–14 (mean 8) years were treated with an antegrade colonic enema procedure. Median follow-up was 32 (range 24–60) months. No differences in morbidity were noted related to age or sex. There were no early postoperative complications.

Faecal continence was achieved in 11 of the 13 patients. Six children required a subsequent operative procedure, five of which were intermediate or major procedures (stoma revision, colostomy) (*Table 1*). Although numbers are small, the flush sutured method appeared better than the 'fish-tailed' sutured procedure (*Table 2*). *Table 3* shows that additional water is often required with this enema

Table 1 Further operations required for failure or complications of the antegrade colonic enema procedure

Operation	No. attempted	No. of subsequent successful operations
Stoma dilatation	3	1
Stoma revision	5	3
Colostomy	2	2

Paper accepted 17 January 1996

Table 2 Morbidity resulting from the formation of an antegrade colonic enema stoma with the three methods used

	Flush sutured	'Fish-tailed' sutured	Caecal
No. of procedures	8	4	1
Stoma leakage (mucous)	2	1	0
Stoma stenosis	2	3	0
Intolerance of enema instillation	0	1	0
Failure of enema regimen	1	0	0
Colostomy	1	1	0

Table 3 Successful enema regimens used in conjunction with the antegrade colonic enema

Enema regimen	No.
Polyethylene glycol alone	4
Additional water	5
Additional water and phosphate enema	1

regimen to overcome the osmotic load induced by the polyethylene glycol.

Discussion

The antegrade colonic enema procedure was introduced for the management of constipation or faecal soiling when conservative methods have failed and a colostomy is being considered[1]. Malone *et al.*[2] described a method in which the appendix is reimplanted into the caecum to create a valve. Reimplantation is complicated and is probably unnecessary. In the present series the appendiceal stump was simply intussuscepted into the caecum to create a valve. Initially a skin tube was used to anastomose the appendix to the skin, but this has now been abandoned due to the high stenosis rate. This retrospective review reveals that, of the 13 children, only seven progressed through this procedure with minor complications (the morbidity rate associated with the flush sutured method was the lowest). However, in the long-term, 11 of the 13 patients attained a level of excellent faecal control, which not only allowed social cleanliness, but appeared to be of great psychological benefit to the patient. In all but one case the patient and family found the stoma easy to manage and it was well tolerated. In one case, although patient compliance was initially poor, the functional result was excellent. Squire *et al.*[1] reported excellent preliminary results for the Malone antegrade colonic enema. The present data confirm these findings of an excellent outcome, albeit in some cases after further surgery.

The present report draws attention to the high overall morbidity rate, six of the 13 patients requiring a subsequent operation after the initial antegrade colonic enema procedure. Five of these children required a further intermediate or major operation; however the majority of problems were related to the skin tube technique and this is now no longer used. Of the five patients with stoma stenosis, stomal dilatation was attempted on three occasions, in one case successfully. The two children with failed dilatations underwent successful stoma revision along with one of two others with stoma stenosis. In one case the operation was unsuccessful to produce a continent cathertizable stoma and required a sigmoid colostomy. One patient required a sigmoid colostomy for symptomatic control due to failure of the enema regimens. Sigmoid colostomy proved effective at symptom management in both these patients.

The enema regimen (*Table 3*), an issue that remains unresolved, was reviewed. Treatment has been on a trial and error basis to date, rather than by rigid guidelines. Phosphate enemas were originally described as the active enema constituent; however phosphate toxicity has been a problem with repeated administration of phosphate-based enemas[6]. With the present enema regimen (0·75–1 litre polyethylene glycol 3350), four patients required no modification of the enema. Six patients required additional water (0·5–1 litre), a modification that appears to help overcome the high residual osmotic load created by the polyethylene glycol. One child required an additional phosphate enema on an intermittent basis to render faecal control and for one child the enema regimen was of no benefit. In our experience the use of a syringe bolus rather than gravity-based infusion is a superior technique of administration with evacuation 30–60 min after administration. This method was used by nine of the present patients with good compliance.

The antegrade colonic enema is an effective method for the treatment of severe intractable constipation and faecal soiling. It is not a replacement for conservative methods, which are effective. It is our view that the best technique is an intussuscepted appendiceal stump sutured flush to the skin.

In this study only two of 13 patients required a colostomy, which all would have needed before the introduction of colonic enema. There were no serious complications with the colonic enema procedure and the eventual outcome was more satisfactory functionally, cosmetically and psychologically than a colostomy. Due to the recent introduction of the antegrade colonic enema, data for long-term follow-up are not available. It is our opinion that the method will remain effective for the management of intractable constipation and faecal soiling as the patient grows.

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British Journal of Surgery 1996, 83, 644–646

Acute right iliac fossa pain in acquired immunodeficiency: a comparison between patients with and without acquired immune deficiency syndrome

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A retrospective review was performed of the clinical features present in 17 patients who were human immunodeficiency virus (HIV) positive requiring a diagnostic or therapeutic procedure for suspected appendicitis. Patients who were acquired immune deficiency syndrome (AIDS) free ($n = 11$) and those with AIDS ($n = 6$) were compared. Ten of the 11 patients who were AIDS-free had appendicitis. The morbidity rate was 9 per cent, similar to that expected in seronegative patients, but the appendix perforation rate was 50 per cent. Only two of the six patients with AIDS had appendicitis. Three suffered from an HIV-related disease process. Computed tomography (CT) was performed in four of the six patients with AIDS, and was considered of diagnostic help in three. In patients with AIDS, the morbidity rate rose to 50 per cent. Surgical decision-making with regard to HIV-positive patients who were AIDS-free with suspected appendicitis should be similar to that for seronegative patients. For patients with AIDS, alternative diagnostic strategies, including preoperative CT, or possibly laparoscopy, should be considered.

The increasing prevalence of human immunodeficiency virus (HIV) infected patients has created new challenges in the management of abdominal pain. The cumulative prevalence of HIV infection in Geneva, Switzerland is 1 per cent[1]. Some 50–90 per cent of patients with acquired immune deficiency syndrome (AIDS) will develop abdominal symptoms, mainly diarrhoea and abdominal pain[2]. Right iliac fossa (RIF) pain is often due to acute appendicitis, but specific AIDS-related diseases, such as Kaposi's sarcoma, non-Hodgkin's lymphoma or cytomegalovirus (CMV) infection of the appendix or ileum must also be considered[3–6]. Twelve per cent of patients with AIDS need an emergency consultation for abdominal pain[7]. In 2–5 per cent surgical exploration is necessary[4,7] with a mortality rate ranging between 2 and 70 per cent, and a morbidity rate between 18 and 26 per cent[3,8,9]. The wide spectrum of morbidity and mortality rates recorded in different studies may be attributed to variations in patient immune status, differences in surgical management and any delays before surgical treatment. Recent advances in the treatment of opportunistic infections must also be considered[3,9,10]. Several studies examining acute appendicitis have suggested differences between patients with and without AIDS[4,6,8,11].

A review was carried out of the case histories of all patients admitted with suspected acute appendicitis who had a diagnostic or therapeutic surgical procedure. The two patient subgroups were compared in order to define guidelines and optimize the management of these patients.

Patients and methods

The case histories were reviewed of all patients who were HIV-seropositive admitted with acute RIF pain. All these patients required a diagnostic or therapeutic surgical procedure in the digestive surgery unit during the 6 years between June 1988 and June 1994.

Identification of patients was based on medical records, and the hospital's current database was consulted, matching for HIV-seropositivity, AIDS and abdominal pain. A register of all outpatients who were HIV-positive was also consulted to discover those who might have been treated for RIF pain.

Patients were divided into two subgroups according to the Centers for Disease Control clinical criteria for HIV infection and AIDS[12] (*Table 1*). The first group, AIDS-free, included HIV-positive patients without AIDS-defining events. The second group, AIDS, included HIV-positive patients with AIDS-defining events.

In this study, the CD4 lymphocyte count was not considered as an AIDS-defining parameter. The following data were recorded: age; sex; risk category; duration of symptoms; clinical status; laboratory values; radiological investigations; intraoperative and histopathological findings; types of surgical treatment and postoperative morbidity and mortality rates.

Results are presented as median (range). Statistical comparison between the groups was carried out with the unpaired Mann–Whitney rank sum test. $P < 0{\cdot}05$ was considered significant.

Results

During the 6 years studied, 17 HIV-positive patients (11 AIDS-free and six with AIDS) were admitted with suspected acute appendicitis and had a diagnostic or therapeutic surgical procedure (laparotomy, laparoscopy or percutaneous drainage). Median age was 33 (range 24–43) years; there were nine men and eight women. Eleven patients had a history of drug addiction; four were homosexual while two had become infected by heterosexual transmission. On admission, both subgroups were found to have a diminished CD4 lymphocyte count; median white blood cell (WBC) count was 3300 in the AIDS subgroup and 8800 in the AIDS-free subgroup (*Table 2*). Postoperative leukopaenia occurred in both patient subgroups.

Seven patients (three AIDS-free and four with AIDS) had preoperative computed tomography (CT). A retrospective analysis of the CT diagnostic performance is shown in *Table 3*. In six patients CT was of diagnostic

Paper accepted 29 August 1995

help, directing the surgeon to an efficient therapeutic procedure. In one patient, laparotomy was delayed as a result of an erroneous CT diagnosis (sigmoiditis).

Mean delay between admission and surgery was 17 h in the AIDS-free patients and 51 h in those with AIDS.

One patient had CT-assisted percutaneous drainage of an RIF abscess. The remaining patients, all of whom presented with a peritoneal reaction localized in the RIF, were explored surgically. A total of 14 laparotomies (McBurney and/or midline incision) and two diagnostic laparoscopies (with incidental appendicectomy in two patients with persistent clinical signs) were performed. In one patient acute salpingitis was diagnosed. In the other no abnormality was detected.

Among patients with AIDS, two of six suffered from appendicitis, one had salpingitis while three had HIV-related conditions: CMV terminal ileitis, Kaposi's sarcoma of the appendix and a *Streptococcus milleri* RIF abscess.

In the AIDS-free patient subgroup, ten of 11 patients suffered from acute appendicitis. In nine, this was proven by histopathological examination. In another the diagnosis of appendicitis was made on the basis of CT findings which showed a RIF abscess. The final patient had normal laparoscopy and the diagnosis remained undetermined.

In total, 12 patients suffered from acute appendicitis; in half the appendix was perforated (one patient with AIDS, five AIDS-free patients). Mean symptom duration was 33 h in patients with non-perforated appendicitis and 73 h in patients with perforation. In two patients, however, perforation occurred within 24 h of the onset of abdominal pain. When perforated appendicitis was diagnosed, antibiotics were administered intravenously.

Table 1 Centers for Disease Control clinical classification system of human immunodeficiency virus infection

Clinical disease criteria
Category A
Acute HIV infection
Asymptomatic HIV infection
Persistent generalized lymphadenopathy
Category B
Bacillary angiomatosis, oropharyngeal candidiasis, cervical dysplasia–cervical carcinoma *in situ*, hairy leukoplakia, herpes zoster, listeriosis, peripheral neuropathy, etc
Category C
Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS: oesophageal candidiasis, candidiasis of bronchi–trachea–lungs, invasive cervical cancer, disseminated or extrapulmonary coccidioidomycosis, extrapulmonary cryptococcosis, chronic intestinal cryptosporidiosis, cytomegalovirus (CMV) disease (other than spleen, liver and nodes), CMV retinitis, HIV-related encephalopathy, herpes simplex, chronic ulcer–bronchitis–oesophagitis–pneumonitis, disseminated or extrapulmonary histoplasmosis, chronic intestinal isosporiasis, Kaposi's sarcoma, Burkitt's lymphoma, immunoblastic lymphoma, *Mycobacterium avium intracellulare* disseminated or extrapulmonary, *Mycobacterium tuberculosis* any site, *Pneumocystis carinii*, pneumonia, recurrent pneumonia, progressive multifocal leukoencephalopathy, *Salmonella* sp. septicaemia, toxoplasmosis of brain, wasting syndrome due to HIV

Patients are diagnosed as having acquired immune deficiency syndrome (AIDS) if classified in category C. HIV, human immunodeficiency virus; CDC, Centers for Disease Control

Table 2 Comparison between patients with and without acquired immune deficiency syndrome

	Patients without AIDS	Patients with AIDS	P‡
Age (years)*	32 (24–39)	35 (28–43)	—
Preoperative WBC count (per mm^3)*	8800 (4600–11700)	3300 (1400–6500)	<0·01
Postoperative WBC count (per mm^3)*	3900 (2000–5500)	1900 (1400–4800)	—
Preoperative CD4 lymphocyte count (per mm^3)*	200 (40–700)	27 (5–299)	<0·05
Diagnosis			
Appendicitis	10 (5†)	2 (1†)	—
HIV-related disease process	—	3	—
Other	1	1	—
No. of patients	11	6	—
Morbidity rate (per cent)	9	50	n.s.

*Values are median (range). †No. of patients with perforated appendicitis. AIDS, acquired immune deficiency syndrome; WBC, white blood cell; HIV, human immunodeficiency virus; n.s., not significant. ‡Mann–Whitney rank sum test

Table 3 Evaluation of the computed tomography results in patients who were human immunodeficiency virus-positive with clinical suspicion of appendicitis

HIV-positive patients	CT diagnosis	Subsequent procedure	Final diagnosis	Retrospective evaluation
AIDS	RIF abscess without appendicular involvement	Diagnostic midline laparotomy	RIF abscess of extra-appendicular origin	Positive
AIDS	Phlegmonous appendicitis	McBurney incision	Phlegmonous appendicitis	Positive
AIDS	Normal appendix, no detected anomaly	Diagnostic laparoscopy	Acute salpingitis	Positive
AIDS	Sigmoiditis	Colonoscopy; delayed McBurney incision	Phlegmonous appendicitis	Negative
AIDS-free	Appendicular abscess	CT-assisted percutaneous drainage	Abscess of appendicular origin	Positive
AIDS-free	Appendicitis	McBurney incision	Acute appendicitis	Positive
AIDS-free	Appendicitis	McBurney incision	Acute appendicitis	Positive

HIV, human immunodeficiency virus; CT, computed tomography; AIDS, acquired immune deficiency syndrome; RIF, right iliac fossa

On day 11 after operation, one of the AIDS-free patients needed transrectal drainage of a pelvic abscess (morbidity rate of 9 per cent). Three of the AIDS patients developed septic complications (morbidity of 50 per cent): herpetic transverse myelitis, atypical mycobacterial pneumonia and *Escherichia coli* septicaemia. There were no perioperative deaths. Mean hospital stay was 8·0 days for the AIDS-free patient subgroup and 9·9 days in the AIDS patient subgroup.

Discussion

In this study, 91 per cent of AIDS-free patients had the diagnosis of acute appendicitis confirmed at operation, without any concomitant HIV-related disease. Fifty per cent of the AIDS-free patients had perforated appendicitis, a high rate previously observed among HIV-positive patients[3]. The only postoperative complication in the AIDS-free patient subgroup was a pelvic abscess, following perforated appendicitis. A 15-fold increase in the risk of developing an abdominal abscess has been observed in perforated appendicitis[13]. The postoperative morbidity rate observed in the AIDS-free patient subgroup (9 per cent) was similar to that of a seronegative population[13], despite leukopaenia and the high rate of perforation. Perioperative broad-spectrum antibiotics and intravenous fluids may have contributed to this low morbidity rate and the absence of mortality. Although more than 10 000 WBC per mm^3 are found in 80 per cent of HIV-negative patients with appendicitis, this diagnostic clue was not present here. Consequently, even in asymptomatic HIV infection, the WBC count cannot be of diagnostic assistance. This low WBC is explained by the depressed immune response, the high frequency of myelodysplasia and zidovudine treatment[11,13].

In this study, diagnostic laparoscopy was performed in two patients with a low clinical suspicion of appendicitis. Laparoscopy has been recommended as a minimally invasive diagnostic and therapeutic procedure which reduces the risk of HIV virus transmission and improves the postoperative course[3,9,13,14]. A thorough intraoperative exploration is mandatory to seek any HIV-related pathology. Any positive finding will lead to AIDS-specific postoperative therapy.

Among AIDS-free patients with acute RIF pain, surgical decision-making should be similar to that for seronegative patients, although early diagnostic laparoscopy might be considered because of the high rate of perforated appendicitis.

In AIDS patients, the differential diagnosis is widened by immunodeficiency-related conditions. Most need medical treatment, and surgery might only be considered in the event of secondary complications[15].

Six patients with AIDS were admitted with suspected appendicitis which was confirmed in only two; in three, RIF pain was attributed to HIV-related pathologies. Four HIV-related diseases may be anticipated in AIDS patients with acute RIF pain: CMV colitis, Kaposi's sarcoma, non-Hodgkin's lymphoma and mycobacterial infection.

The challenge is to diagnose HIV-related conditions before surgery; laparotomy should be used only to confirm acute appendicitis or any other condition requiring surgical treatment. In this study the mean delay of 2 days between admission and surgery was probably an indirect reflection of the difficulties in surgical decision-making. Signs and symptoms were often non-specific and gastrointestinal symptoms were common[2].

CT was performed in four of six patients, and in three lent precision to the diagnosis and helped to determine the surgical strategy. Consequently routine complementary investigation should be encouraged. CT with intravenous contrast injection narrows the differential diagnosis[16]. Further diagnostic procedures, if available, have to be carried out once the site of involvement has been localized. In cases of RIF abscess of appendiceal origin, CT-guided percutaneous drainage should be considered[17]. Laparoscopic surgery, which seems to be well tolerated in AIDS patients with acute appendicitis, is also a possibility[14].

Acknowledgements

Thanks are due to Professor B. Hirschel, Division of Infectious Diseases, University Hospital of Geneva, Switzerland for his advice.

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British Journal of Surgery 1996, **83**, 647

Case report

Two cases of solitary metastases from carcinoma of the lung presenting as primary colonic tumours

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There have been no reports in the literature of solitary colonic metastases from primary tumours elsewhere without any other signs of disseminated disease apparent at the time of diagnosis of the colonic lesion. Here we present two cases of solitary colonic metastases from carcinomas of the lung presenting as a primary colonic tumour.

Case report

Patient 1

A 60-year-old woman had undergone left pneumonectomy 1 year previously for squamous carcinoma of the lung without evidence of lymph node involvement or disseminated disease. She presented with a short history of rectal bleeding, and at colonoscopy a 5-cm stenosing lesion was found at the splenic flexure. There was no mucosal abnormality, and the compression appeared extrinsic. Investigations showed no evidence of metastatic disease. An extended right hemicolectomy was performed, with an uneventful recovery. Histological examination showed a metastatic squamous carcinoma without lymph node involvement. The patient died 2 years later from disseminated metastases.

Patient 2

A 52-year-old woman had a left upper lobectomy for a coin lesion seen on chest radiography. Histological examination showed adenosquamous carcinoma with no lymph node involvement. The patient remained well for 6 months before developing rectal bleeding, left-sided abdominal pain and a left upper quadrant mass. Colonoscopy revealed a large tumour at the splenic flexure with extramucosal occlusion of the lumen and a small friable exophytic lesion visible on the mucosa; barium enema confirmed the stenosis. There was no evidence of metastatic disease. An extended left hemicolectomy was performed, with an uneventful recovery.

The specimen showed an 8-cm stenosing intramural lesion with a small pedunculated polyp in its centre (*Fig. 1*). Histological examination demonstrated metastatic adenosquamous carcinoma with no lymph node involvement plus a coincidental tubulovillous adenoma. The patient remains well 2 years later.

Discussion

Metastatic lesions in the colon have been reported in the past, but the patients have had evidence of dissemination of the primary disease at the time of gastrointestinal presentation. These two patients had no evidence of spread from the primary carcinoma of the lung and presented with a second primary tumour of the colon. Both patients had stenosing intramural lesions at the splenic flexure with no positive lymph nodes.

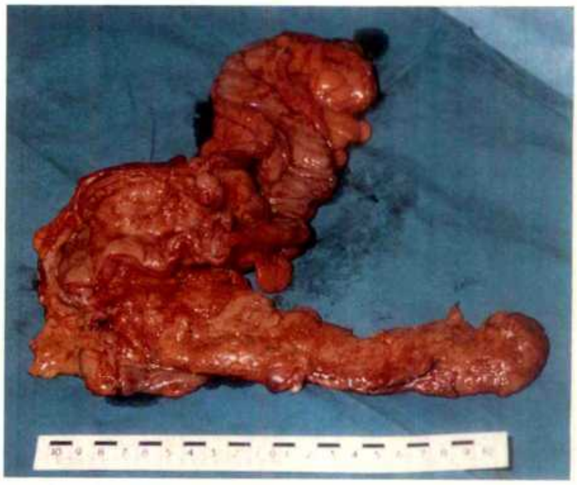

Fig. 1 Surgical specimen from patient 2, showing constricting lesion and incidental tubulovillous adenoma

Voravud *et al.*[1] reported breast cancer metastasizing to the splenic flexure of the colon in a patient with confirmed lymph node spread and bony metastases. There was a past history of colonic polyps and a family history of colorectal carcinoma. Santoro and colleagues[2] described a patient with multiple metastatic deposits in the colon from a malignant fibrous histiocytoma, who presented with lower gastrointestinal bleeding. The patient had had a colonic carcinoma resected 11 years earlier and had coincident lung metastases. By contrast, the two patients in the present report had had 'curative' excision of the original carcinoma of the lung, and following resection of the colonic metastases there was no further spread for 2 years, when one patient developed lung metastases.

In all these cases the metastases were confined to the wall of the colon, with no invasion of adjacent structures. In all except one there had been a past history of colonic disease (or an incidental colonic polyp), suggesting some form of underlying predisposition to the development of colonic metastases. The predilection to metastasize to the splenic flexure is unexplained.

In conclusion, patients who present with a suspected colonic neoplasm and a past history of another malignancy should be considered to have possible metastatic disease, especially if the constriction appears extramucosal and the lesion is at the splenic flexure. If the colonic lesion is a squamous carcinoma, an extracolonic source should be sought as primary squamous carcinoma of the colon is extremely rare[3].

Paper accepted 19 September 1995

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British Journal of Surgery 1996, **83**, 648–651

Role of segmental colonic transit time studies to select patients with slow transit constipation for partial left-sided or subtotal colectomy

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This prospective study investigated the value of segmental colonic transit time studies in the surgical treatment of slow transit constipation. Overall, 346 patients with chronic constipation were analysed; slow transit constipation was diagnosed in 86 (25 per cent). Based on the results of segmental colonic transit time studies, 18 patients underwent partial left-sided colectomy and 24 subtotal colectomy. Recurrent constipation was seen in three of 18 patients and seven of 24 respectively. Severe abdominal discomfort was noted in six of 18 and 15 of 24 respectively. Disabling diarrhoea and faecal incontinence developed in two of 14 and five of 20 patients with an anastomosis respectively. Although these results indicate that segmental colonic transit time studies are useful in selecting patients with slow transit constipation for partial left-sided or subtotal colectomy, both procedures should be performed with prudence.

Patients with slow transit constipation have infrequent defaecation with two or fewer bowel actions each week. Although they have a normal-sized colon, the colonic transit time is markedly prolonged. Most patients present with a general sense of malaise, bloating, abdominal pain, nausea and vomiting, which interferes with the ability to work and to enjoy social activities. Dietary measures and medical treatment including laxatives and enemas fail to relieve these distressing symptoms. This syndrome is confined almost entirely to women[1]. Subtotal colectomy is advocated when conservative measures have failed and surgical intervention is finally considered[2–4].

There are embryological, histological and functional differences between the right and left parts of the colon[5]. Furthermore, isolated left-sided colonic dysfunction following surgery for rectal cancer and after spinal cord injuries has been reported[6,7]. Segmental colonic transit time studies are advocated to distinguish between patients with total colonic inertia, left-sided colonic inertia and anorectal outlet obstruction[8–10]. Despite these facts, no prospective study has been performed using segmental colonic transit times to select patients for partial colectomy.

This prospective study investigated the role of segmental colonic transit times in the decision-making process before surgery for slow transit constipation and compared the results of partial left-sided colectomy with those of subtotal colectomy.

Patients and methods

Between May 1985 and December 1994, 346 patients with severe long-standing constipation and disordered defaecation were analysed according to a standard protocol. This protocol included the patient's history, results of physical, biochemical and endoscopic examination, findings at barium enema, anorectal manometry, full-thickness rectal biopsy, electromyography of the pelvic floor, defaecography and segmental colonic transit time studies. To determine segmental colonic transit time the method described by Arhan *et al.*[11] was used. From at least 2 days before the start of the transit time study, patients stopped taking laxatives, enemas, prokinetic agents and any other drug that could possibly influence colonic transit. No dietary changes were made. Subtotal colectomy was advised when the progression of markers was delayed in all segments of the large bowel and partial left-sided colectomy when transit in the right part of the colon was normal.

Slow transit constipation was diagnosed in 86 patients (25 per cent). Forty-eight patients with such constipation underwent colonic resection. Four patients were followed up for less than 12 months. A further patient needed a terminal ileostomy after breakdown of the ileorectal anastomosis. One patient died shortly after the operation from mesenteric infarction. The remaining 42 patients, 40 women and two men of mean age at operation 47 (range 17–73) years, were available for follow-up of at least 1 year. The mean follow-up was 46 (range 12–80) months.

Before operation all patients were constipated with a median interval between spontaneous bowel movements of 20 days (range 3 days to no defaecation at all), of 7 days between bowel movements with the help of laxatives (range 3 days to no defaecation at all) and of 7 days between bowel movements with the help of enemas (range 1 day to no defaecation at all). All patients had used a variety of laxatives and 21 had used enemas regularly. Clinical features are shown in *Table 1*. The median duration of symptoms was 18 (range 1–70) years.

At follow-up, patient satisfaction was assessed and functional results classified according to the system shown in *Table 2*. In patients with an anastomosis, recurrent constipation was defined

Table 1 Clinical features before and after colonic resection for slow transit constipation

		After colectomy	
	Before operation (*n* = 42)	Partial left-sided (*n* = 18)	Subtotal (*n* = 24)
Constipation	42	3	7
Use of laxatives	42	3	5
Use of enemas	21	0	0
Abdominal pain	38	6	15
Nausea	29	4	12
Vomiting	22	2	10
Bloating	34	4	12
Disabling diarrhoea	0	1	3
Faecal incontinence	0	1	2

Paper accepted 1 October 1995

as a stool frequency of less than two a week. In patients with a stoma, recurrent constipation was defined as irregular non-daily production of faeces. Regular use of laxatives and enemas was also considered to be a sign of recurrent constipation. Daily incapacitating abdominal pain, bloating, nausea and vomiting were classified as severe abdominal discomfort. Recurrent constipation, severe abdominal discomfort as well as disabling diarrhoea and faecal incontinence were considered as failures. Abdominal complaints not interfering with daily life and occurring less than once a week were defined as mild abdominal discomfort and not classified as a failure (*Table 2*).

Results

Based on the results of segmental colonic transit time studies, 18 patients underwent partial left-sided colectomy and 24 subtotal colectomy. A primary anastomosis was constructed in 14 patients after partial left-sided colectomy and in 20 after subtotal colectomy. An end stoma was created in the remaining patients, who had poor anal function. Postoperative clinical features are shown in *Table 1*. Recurrent constipation was seen in three of 18 patients following left-sided colectomy and in seven of 24 after subtotal colectomy. Postoperative disabling diarrhoea and faecal incontinence occurred in respectively two of 14 and five of 20 patients who had an anastomosis (*Table 3*). In patients who developed recurrent constipation, the symptoms recurred in 80 per cent within 1 year of the operation. Severe abdominal discomfort recurred within 15 months in 90 per cent of those affected (*Figs 1* and *2*).

After partial left-sided colectomy and subtotal colectomy 12 of 18 patients and 15 of 24 respectively expressed satisfaction with the outcome.

Table 2 Scoring system for the evaluation of functional results

	Success	Failure
Recurrent constipation	−	+
Stool frequency < 2 times weekly		
Irregular non-daily stoma production		
Regular use of laxatives		
Regular use of enemas		
Mild abdominal discomfort	+	−
Mild abdominal complaints occasionally		
Not interfering with daily life		
Severe abdominal discomfort	−	+
Bloating, nausea, vomiting		
Daily and disabling abdominal pain		
Disabling diarrhoea	−	+
Faecal incontinence	−	+

Table 3 Functional results after colonic resection for slow transit constipation

		Failures		
	Successes	Recurrent constipation	Severe abdominal discomfort	Disabling diarrhoea and faecal incontinence
Colectomy				
Partial left-sided	12 of 18	3 of 18	6 of 18	2 of 14
Subtotal	8 of 24	7 of 24	15 of 24	5 of 20

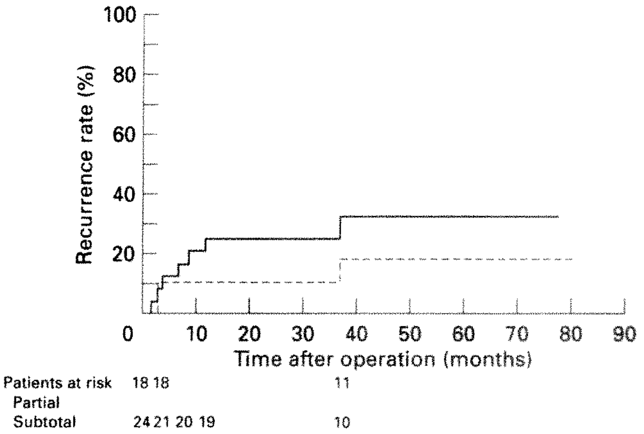

Fig. 1 Recurrent constipation after partial left-sided (– – –) and subtotal (———) colonic resection for slow transit constipation (Kaplan–Meier analysis)

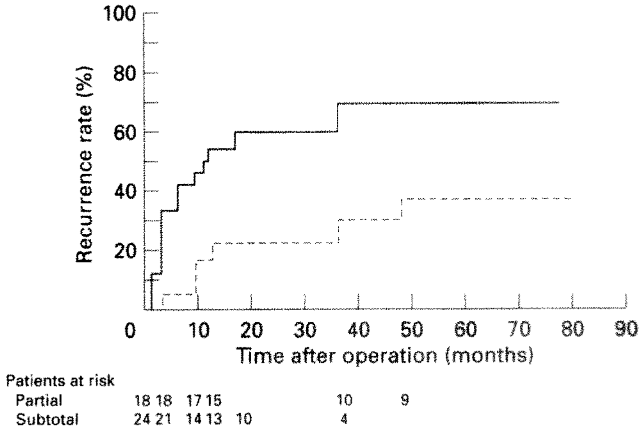

Fig. 2 Severe abdominal discomfort after partial left-sided (– – –) and subtotal (———) colonic resection for slow transit constipation (Kaplan–Meier analysis)

Small bowel obstruction developed in one patient and required division of adhesions, after which she did well. In one patient repeat laparotomy was performed because of severe abdominal discomfort. During laparotomy mild dilatation of the terminal ileum was observed and a terminal ileostomy was created. After operation there was daily regular stoma production, but the severe abdominal discomfort persisted.

Discussion

At the beginning of this century, Arbuthnot Lane[12] was probably the first to perform colectomy with ileorectal anastomosis in patients with slow transit constipation. Initially patients were selected for the operation largely according to the severity of symptoms[3,15–20]. During the past two decades, whole gut transit time studies, using radio-opaque markers, have been added for selecting possible candidates for surgery[2,4,21–34]. To date over 20 papers have been published on the functional outcome of colonic resection in a total of 443 patients[2–4,12–34]. The vast majority (372) of these patients underwent subtotal colectomy, which was successful in 289 (78 per cent). In 71 patients partial colectomy was performed with good functional outcome in 57 (80 per cent). Although these results are similar, most surgeons perform subtotal colectomy, mainly based on the recommendations of Preston *et al.*[2], who concluded that subtotal colectomy was successful in 11 of 16 patients. However, eight of these 16 continued having abdominal pain, ten having bloating and six episodes of faecal incontinence after operation. These symptoms were not included in the evaluation of clinical outcome. Five further patients underwent partial colectomy; in two of these partial left-sided colectomy was performed and in three sigmoid resection. The indication for partial colectomy was not given and none of the patients was selected on the basis of segmental colonic transit time studies. In contrast to the detailed discussion regarding clinical outcome after subtotal colectomy, it was stated only that patients after partial colectomy did not improve. In our opinion, it is remarkable that the recommendation to perform subtotal colectomy is based only on this single study.

Embryologically the proximal part of the colon originates from the midgut and the distal part from the hindgut. The proximal and distal parts are innervated and vascularized in different ways. The right colon has mainly resorptive capacities whereas the left colon has storage capacities[5]. Decreased motility in the left part of the colon has been observed following surgery for rectal cancer and after spinal cord injury[6,7]. A similar motility disorder, restricted to the left part of the colon, has also been reported in patients with slow transit constipation[1,35,36]. These patients could benefit from partial left-sided colectomy, which has the advantage over subtotal colectomy of retaining some storage and resorptive capacity, thereby avoiding diarrhoea.

In 1969 radio-opaque markers were introduced to measure whole gut transit time[37]; segmental colonic transit time can also be estimated with this technique[10,38]. This has been shown to be a reproducible method[37,39]. More recently, radioscintigraphy has been introduced to assess total and segmental colonic transit time[11,40]. It was demonstrated that radioisotope and radio-opaque marker methods gave similar results[40]. Both methods are useful in classifying patients with slow transit constipation as having total colonic inertia, partial left-sided colonic inertia or anorectal outlet obstruction[8–10,40]. Previously segmental colonic transit time studies have been used only to exclude patients with anorectal outlet obstruction. Surprisingly however, only in one retrospective study were segmental colonic transit time studies used to select two patients for partial left-sided colectomy; both patients improved[29]. In two other reports the results of segmental colonic transit time studies are mentioned. However, in all patients subtotal colectomy was performed[4,30].

In the present study patients underwent subtotal colectomy only when the progression of markers was delayed in all segments of the large bowel. If transit in the right part of the colon was normal, partial left-sided colectomy was performed. If transit was delayed only in the rectosigmoid region, anorectal outlet obstruction was diagnosed and no colectomy was performed. The results of this prospective study indicate that the clinical outcome is similar in the two groups undergoing resection.

The present results seem less favourable than those reported by others. From our point of view, evaluation of clinical outcome should be based on four criteria: recurrent constipation, severe abdominal discomfort, disabling diarrhoea and faecal incontinence (*Table 2*). Other studies indicate that subtotal colectomy usually produces improvement as defined by more frequent stools. However, many patients continue to have abdominal pain, bloating, nausea and vomiting. Furthermore, diarrhoea and faecal incontinence also decrease quality of life considerably and should be taken into account. In only three studies have these criteria been evaluated[20,27,28]; the present results are similar to those obtained in these.

To determine the final outcome after surgical treatment of slow transit constipation long-term follow-up is recommended by most authors. In this study, however, it was found that constipation recurred within the first 12 months in 80 per cent of the recurrences and severe abdominal discomfort recurred within the first 15 months in 90 per cent of those affected. This suggests that the benefit of surgery tends to be maintained, which is supported by the findings of Kamm *et al.*[27].

In our opinion, segmental colonic transit time studies are a useful tool to select patients with slow transit constipation for partial left-sided or subtotal colectomy. Because the clinical outcome of partial left-sided colectomy is similar to that of subtotal colectomy such limited resection should be taken into account if progression of markers is normal in the right part of the colon. Because of the moderate functional results, both procedures should be performed with prudence.

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British Journal of Surgery 1996, **83**, 652–653

Response to regional chemotherapy in patients with variant hepatic arterial anatomy

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Regional chemotherapy for colorectal liver metastases is conventionally delivered by a catheter inserted into the gastroduodenal artery. However, up to 40 per cent of patients have 'unconventional' hepatic arterial anatomy. The response rate to regional chemotherapy was examined in 28 patients with normal and in 17 with variant hepatic arterial anatomy. There was no significant difference in response rates between the two groups.

The outlook for patients with colorectal liver metastases remains poor[1]. Despite the recent addition of folinic acid to 5-fluorouracil (5-FU) the results of systemic chemotherapy remain disappointing because, although response rates are increasing, survival is not significantly prolonged[2].

Regional chemotherapy for liver metastases via a surgically introduced hepatic artery catheter achieves higher drug concentrations in the liver with decreased systemic spill and decreased systemic toxicity. Although the response rate is increased compared with that of systemic treatment, as yet there is no convincing evidence that survival is prolonged.

One of the problems encountered in the surgical implantation of hepatic artery catheters is that up to 40 per cent of patients have 'unconventional' hepatic arterial anatomy[3]. Conventionally, a catheter is placed into the gastroduodenal artery, but if variant anatomy is present, the accessory vessel has to be ligated or dual catheters inserted[4]. This can make the procedure technically more complex and it has been suggested that patients with variant anatomy have a poorer response to chemotherapy than those with conventional anatomy[5].

The aim of this prospective study was to assess whether unconventional anatomy results in a significantly poorer response to intra-arterial chemotherapy.

Patients and methods

Forty-five patients with colorectal liver metastases had preoperative angiography to demonstrate the anatomy which was subsequently confirmed at laparotomy. The percentage hepatic replacement was calculated using image analysis computed tomography (CT). Twenty-eight patients had normal hepatic arterial anatomy and in these a silicone catheter (Infusaid, Norwood, Massachusetts, USA) was inserted into the gastroduodenal artery and perfusion of the whole liver confirmed by injection of patent blue dye (Guerbert, France).

Seventeen patients had variant anatomy. In seven the hepatic arterial supply was from the coeliac axis. In one patient the gastroduodenal artery arose from the right hepatic artery and a catheter was placed into the gastroduodenal artery; the left hepatic artery was ligated. Two of six patients with a trifurcation had a catheter inserted retrogradely into the splenic artery until its tip lay at the common hepatic artery, while in the remaining four a saphenous vein graft was applied proximally to the bifurcation of the common hepatic artery[4].

Ten patients had a dual blood supply. The right hepatic artery arose from the superior mesenteric artery in eight: three had the right hepatic artery ligated and five had dual catheters inserted. The right hepatic artery was ligated in two patients with right and left hepatic arteries arising separately from the coeliac trunk. A large accessory vessel arising from the left gastric artery in one patient with dual anatomy was ligated. In all patients adequate perfusion of both lobes was confirmed by patent blue dye injection at the time of surgery.

All patients received intra-arterial 5-FU (1·5 g/m^2 as a 24-h infusion) and systemic folinic acid (200 mg/m^2 as a 2-h infusion immediately before and after 5-FU infusion) weekly for 6 weeks, followed by a 2-week break and repeat of the cycle. CT was performed before operation and at 3-month intervals. Treatment continued until there was objective evidence of disease progression, or when systemic toxicity occurred and did not respond to dose reduction. Response rates were defined using World Health Organization criteria: complete response (no residual tumour visible); partial response (more than 50 per cent decrease in size); stable disease (no worsening of disease or the appearance of new metastasis); and progressive disease (more than 25 per cent increase in size).

Results

Twenty-eight patients had normal anatomy and 17 variant anatomy. Response rates, percentage hepatic replacement and duration of response are shown in *Table 1*. Patients with a complete or partial response were classified as responders, and those with stable or progressive disease as non-responders.

No significant difference in response between patients with normal and variant hepatic arterial anatomy was observed ($P > 0{\cdot}6$, χ^2 test). Systemic toxicity occurred in 16 patients. Nausea, vomiting and diarrhoea were the most

Table 1 Response rates of patients with normal and variant hepatic arterial anatomy to regional chemotherapy

	Hepatic arterial anatomy		
	Normal	Variant	*P*
Responders	12	6	
Non-responders	16	11	0·62*
Hepatic replacement (%)	12	10	0·15†
Time to progression (months)	6·5	10·0	0·127†

*χ^2 test; †Mann–Whitney *U* test

Paper accepted 17 July 1995

frequent symptoms but the effects were mild with no cases of grade IV toxicity.

Local toxicity attributable to arterial perfusion of chemotherapeutic agents was observed in four patients. Haematemesis from duodenal ulcer or duodenitis was seen in three patients, one patient requiring an emergency Pólya gastrectomy. One patient developed an asymptomatic chemical hepatitis. Two further patients developed liver abscesses which responded to antibiotics and percutaneous drainage.

Discussion

Some 40 per cent of patients undergoing hepatic artery catheterization have variant arterial anatomy[3] arising from either the coeliac axis or superior mesenteric artery. Simple placement of a catheter into the gastroduodenal artery will not produce adequate perfusion of the liver, and a further surgical procedure to ensure perfusion of both lobes of the liver needs to be performed.

It has previously been suggested that the response to intra-arterial chemotherapy is lower in patients with variant anatomy[5], presumably beause of inability to perfuse the whole liver, resulting in progression of disease in the non-perfused areas. This study has demonstrated that, if care is taken to ensure that both lobes of the liver are perfused, there is no significant difference in response to regional chemotherapy in this group of patients compared with that in those with normal anatomy.

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British Journal of Surgery 1996, 83, 654–658

Aortic prosthetic infection: 50 patients treated by radical or local surgery

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Fifty patients with aortic prosthetic infection were managed in a period of 10 years from 1983 to 1993. Twenty-five patients had recurrent sepsis after local surgery (group 1) and 22 of these eventually required radical surgery. Twenty-five patients had radical graft excision as the first procedure (group 2). Group 1 contained an excess of patients with local groin symptoms (11 in group 1 *versus* five in group 2, $P = 0\cdot03$) and in this group fewer radiological techniques were used to document the extent of graft infection. The perioperative mortality rate was similar in both groups (seven in group 1 *versus* five in group 2). The number of amputations was also similar (five in group 1 *versus* four in group 2). The triad of occlusive disease, aortobifemoral bypass and groin symptoms was associated with eight of nine amputations. While the authors would consider using local techniques if the anastomosis was intact, the graft remained patent and infection appeared to be confined to the groin, this combination is uncommon and radical graft excision remains the preferred treatment.

The mortality rate associated with aortic graft infection may be as high as 77 per cent[1–4] and amputation rates range from 11 to 57 per cent[1,2,4–6]. Presentation may be soon after graft insertion or delayed for several years[7]. Sterile grafts may become infected by an episode of bacteraemia at any time, but occult infection at the time of graft insertion is probably commoner[1,8,9]. This incidence of graft infection is approximately 1 per cent[1,3,10,11], which means that most vascular surgeons manage only a handful of cases during a professional career. Controlled trials are not feasible and the literature is dominated by anecdotal reports. Discussion has centred on whether it is always necessary to remove a contaminated prosthesis completely and perform an extra-anatomic bypass to restore circulation or whether a lesser procedure might suffice[12–14]. Graft irrigation with antiseptic or antibiotic solution has been advocated as an alternative to total excision[15,16]. The debate should perhaps more properly be about the selection of patients for whom local treatment might be successful. The St Mary's Hospital Vascular Surgical Unit has accumulated an experience of infected grafts implanted in this hospital and elsewhere; the management of 50 patients is described.

Patients and methods

Fifty patients were treated for aortic prosthetic infection from 1983 to 1993. Information was obtained from the operating theatre register, computerized audit and case records. Summaries had been made of the major inpatient episodes occurring at the referring hospital, where applicable. Operating time was obtained from anaesthetic records. It was not possible to obtain the costs of treatment in other hospitals and so estimates of cost at 1994 prices in St Mary's Hospital were used as an approximation of the resource implications for any referring unit. Follow-up data for a minimum of 2 years were obtained at outpatient clinics and through enquiries to general practitioners, where appropriate.

Patients were divided into two groups: patients in group 1 initially had local surgery for graft sepsis and those in group 2 had primary radical surgery and extra-anatomic bypass. For the purposes of this study local surgery was defined as any operative procedure to deal with an infected aortic prosthetic graft other than radical excision. This included irrigation, partial excision and *in situ* replacement. All procedures related to the infected graft, such as wound debridement, amputation, laparotomy etc., were studied. All patients had an infection of Szilagyi grade III at the time of radical excision in this hospital[1].

The Mann–Whitney U test was used to compare numerical data. Fisher's exact test or a one-way χ^2 test with Yates' correction was used to compare frequency data.

Surgical techniques

The authors' preferred management has been bilateral axillofemoral bypass followed immediately by excision of the infected graft, unless there are clear indications, such as haemodynamic instability, to do otherwise. Bilateral grafts are employed to prevent incursion into potentially infected territory in the lower abdominal wall. The grafts are inserted and then the femoral artery proximal to the groin anastomosis is clamped. The axillofemoral grafts supply the legs from then on. The abdomen is opened, the entire aortic graft excised, the aortic stump closed, the retroperitoneal space debrided and the common iliac arteries ligated or oversewn. Care is taken to close the aortic stump with at least two layers of interrupted non-absorbable monofilament sutures inserted into healthy uninfected aorta. This may require suprarenal aortic control. Wrapping the stump in omentum or a vascularized pedicle graft of jejunum may be useful[17]. The gut is repaired in patients who also have an aortoenteric fistula. Occasionally, gentamicin beads are placed inside a fenestrated tube drain laid in the retroperitoneal space for 5 days[13,18,19], or this space may be irrigated with gentamicin solution[16]. Once all the old prosthetic material has been excised, the femoral clamps are removed. In this way perfusion of the pelvis and buttocks is restored by retrograde perfusion of the external and internal iliac arteries when these are patent. Systemic antibiotic therapy is guided by bacteriological culture reports, but broad-spectrum cover against Gram-negative, Gram-positive and *Staphylococcus aureus* coagulase-negative organisms is commenced immediately on diagnosing graft sepsis. Multiple specimens are sent for immediate staining and culture at the time of surgery. A policy of staged graft removal has not been adopted[20]; the principles of radical treatment have remained largely unaltered during the period described in this paper.

Results

No significant difference between patients in groups 1 and 2 was found with regard to age, sex, past medical history,

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Paper accepted 28 August 1995

indications for original operation or type of aortic surgery. Mean age of patients at initial operation was 62 years in group 1 and 63 years in group 2. There was no significant difference between the groups regarding age at presentation with an infected graft: 66 years in group 1 *versus* 68 years in group 2. Primary graft infection presented beween 3 weeks and 19 years after the original operation. Numbers of patients with occlusive disease (11 in group 1 *versus* 13 in group 2), aneurysmal disease (14 *versus* 12 respectively) and groin anastomosis (16 *versus* 12) were similar in both groups. The groups were also alike with regard to presence of hyperlipidaemia, hypertension, smoking history and diabetes mellitus.

The groups were compared with respect to symptoms at the time of presentation with graft infection. No difference was found in terms of sepsis (e.g. pyrexia or rigors), abdominal or back pain, and gastrointestinal haemorrhage. There was, however, a marked difference in the number of patients presenting with groin symptoms (false aneurysm, sinus, haemorrhage) (*P* = 0·03). Eleven patients with groin symptoms initially had local surgery and five had primary radical surgery. There was no difference when comparing the groups for erythrocyte sedimentation rate, white cell count, haemoglobin or serum albumin concentrations. The mean number of inpatient days required to treat graft infection was 80 for patients in group 1 and 56 for those in group 2 (*P* < 0·001) (*Table 1*). There was no difference between the groups with regard to length of stay attributable to radical surgery: 51 days in group 1 *versus* 46 days in group 2. The excess days for group 1 all derived from time spent attempting to treat graft infection by local means. The total number of hospital admissions for inpatient treatment was 2·8 in group 1 and 2·1 in group 2 (*P* = 0·06) (*Table 1*). The total duration of illness from suspicion of graft sepsis to discharge home well was significantly higher in those who had failed local surgery. The mean 'illness time' was 86 weeks in group 1 and 12 weeks in group 2 (*P* < 0·001) (*Table 1*).

The range of techniques used for imaging in referring hospitals before local surgery was similar to that used in this centre, but multiple imaging procedures were less frequently performed in the former. Of 18 patients treated elsewere before referral 12 had undergone angiography, six had had computed tomography (CT) and four an indium-labelled white cell scan; all three of these techniques were used in only six patients. In the St Mary's unit all patients had angiography, CT and an indium-labelled white cell scan if the extent of the infection was unclear. Sometimes the clinical situation in unwell patients with deep graft sepsis made delay undesirable and imaging was then used selectively. Thirty-five patients underwent angiography to delineate anatomy before surgery; only four had an abnormality consistent with infection. Forty-four patients had CT; 28 had an abnormality suggesting infection. In 19 patients a ^{111}In-labelled white cell scan was performed and 15 were positive. Eighty per cent of patients treated in this unit underwent multiple imaging procedures before surgery. Radical surgery has not yet been performed on a patient with supposed 'local' graft sepsis without finding evidence of more widespread infection.

Table 1 Comparison of number of admissions to hospital, inpatient days, number of operations and duration of illness

	Group 1	Group 2	*P**
Mean no. of admissions	2·8 (3·0; 1–6)	2·1 (3·0; 1–6)	0·06
Mean no. of inpatient days	80 (66; 12–204)	56 (33; 10–275)	<0·001
Mean no. of operations	5·0 (4·0; 1–9)	2·2 (2·0; 1–10)	0·002
Mean duration of illness (weeks)	86 (44; 26–936)	12 (6; 2–48)	<0·001

Values in parentheses are median and range. *Mann–Whitney *U* test

Eighteen patients from group 1 had already undergone local surgery for graft sepsis before being referred to this unit. Of 32 patients who had all their treatment for graft infection performed at St Mary's, ten had a local procedure. Initially, five of these ten patients had the whole tube graft replaced *in situ*, but all five later required radical surgery. Two of the ten patients who presented with an aortoenteric fistula were judged to have no prosthetic graft infection and had an *in situ* repair of the fistula; both patients later required radical surgery. A further three patients were treated by graft irrigation with antibiotics alone, without excision of prosthetic material; these patients eventually died from graft sepsis and systemic complications. Hence all ten patients treated entirely at this unit with local techniques either failed to respond to initial measures or re-presented with further widespread graft infection. A total of 47 patients (group 1, 22; group 2, 25) underwent radical graft resection and reconstruction.

Aortoenteric fistulas

Twenty-eight patients had an aortoenteric fistula. Sixteen communicated with the duodenum, ten with other sites in the small bowel and two with the colon. No fistula was diagnosed by endoscopy. Group 1 contained 12 fistulas and group 2 16 (*P* > 0·05).

Follow-up

The longest survivors have been alive and well for 7 years and the authors are unaware of any aortic stump disruption. All patients have been followed for at least 2 years but five were lost to follow-up between 2 and 6 years. No further details have been traced for these patients; five of 38 survivors represents 13 per cent of the surviving population.

Bacteriology

Bacteriology is summarized in *Table 2*. There were no differences between the groups in terms of organisms

Table 2 Bacteriological growth from different regions

Organism	Graft	Blood	Wound
Bacteroides	1	—	—
Citrobacter	2	—	—
Diphtheroids	1	—	1
Escherichia coli	12	—	4
Klebsiella	1	1	—
Proteus	6	1	2
Pseudomonas	4	1	2
Staphylococcus aureus			
Coagulose positive	5	—	2
Coagulase negative	8	—	1
Streptococcus	5	—	—
Streptococcus faecalis	4	—	—
Mixed growth	5	—	3

cultured. It was not possible to culture pathogens from ten of the 47 excised grafts. In four of these cases graft cultures were negative but the patients had discharging groin sinuses. It was assumed that the graft was infected with the same organisms as were present in the groin sinuses. *Escherichia coli* was the commonest organism grown from culture of graft material and was the commonest pathogen in those with an aortoenteric fistula. Blood and wound cultures were performed as appropriate but were usually negative. Two of the three patients who had irrigation treatment alone had a positive bacteriology due to *Salmonella* and coagulase-negative *S. aureus* respectively. The third patient treated with irrigation alone had negative bacteriology cultures.

Major outcome

Major outcomes were as follows. Five patients in group 1 underwent limb amputation; one of these patients had a bilateral above-knee amputation. Four patients in group 2 had limbs amputated. Occlusive disease, groin anastomosis and infected groins were all associated with a higher risk of amputation. Of the 14 patients who presented with this triad, eight required a major amputation. The only patient with aneurysmal disease (one of 26) who required an amputation had an anastomosis in the groin and this was the only amputation performed in a patient without the typical 'triad'. Of the 22 patients in group 1 who had a radical graft resection, seven died. Five of the 25 patients in group 2 died. The common mode of death in both groups was multiple system organ failure.

There has been only one case of recurrent infection following radical surgery within 2 years (one of 38 survivors at 2 years). This patient, with bilateral axillofemoral bypasses, re-presented with an exposed mid-portion of one axillofemoral graft 6 months after its insertion. The infection had occurred at the site of a midgraft staging incision, which is an incision that the authors now avoid by using a long tunneler. The infected axillofemoral graft was removed and a femorofemoral crossover bypass formed, converting the uninfected unilateral axillofemoral bypass into an axillobifemoral bypass. There have been no other documented recurrences in the 35 patients who have had longer-term follow-up.

Estimated costs of inpatient management were obtained from St Mary's Hospital and may be regarded as reflecting costs elsewhere at 1994 prices. There were significant differences between groups 1 and 2 in operating theatre costs ($P<0\cdot01$) and inpatient costs ($P<0\cdot02$); the total cost per patient (at 1994 prices) was £29 733 in group 1 and £24 377 in group 2 ($P<0\cdot01$). Costs before referral to this centre, for intensive care, dialysis, imaging etc., were not included in these estimates and the cost difference expressed above is, therefore, a conservative figure. Prolonged illness is responsible for an inability to work in some patients. No attempt was made to estimate this hidden cost over an additional 74 weeks per patient in group 1.

Discussion

Death and morbidity rates from aortic graft infection are high[1–4,20,21]. Recent reports suggest that the results of treatment of this complication are improving, with better imaging and perioperative care[4,20]. The 'gold standard' treatment has been radical removal of the infected graft with extra-anatomic bypass to the lower limbs[4,20]. Recently, there have been reports of less extensive surgery[12,13,22] or irrigation regimens with claims of good outcome[15,16,23–26]. The numbers treated by these latter techniques are small and long-term follow-up is not always available. Irrigation techniques are suggested for those patients who are at 'high risk' or 'not suitable' for radical surgery[15,16,23,24]. Undoubtedly local surgery is occasionally successful but, as has been shown in previous studies, recurrent graft infection is to be expected in 22–100 per cent of cases, depending of the technique used[4,27]. Some authors consider that infection usually starts at the time of graft implantation and, if this is so, recurrence of infection following partial excision seems inevitable[6].

The present study does not compare local and radical surgery directly, but highlights the fate of those who undergo local therapy that fails. Many patients referred to this unit had undergone inappropriate local procedures and some lessons may be learned from this. The first is that failure to appreciate the extent of infection occurs because of inadequate imaging. The extent of graft infection is not revealed by angiography. In the present series angiography was sometimes the only radiological investigation performed before local surgery, but in only four of 35 cases did it show evidence of deep infection. Obviously angiography should not be relied upon as the sole imaging technique. Both CT and a radio-isotope technique should be used to determine the extent of graft infection before declaring that the infection is local. Contrast-enhanced CT should be the first investigation since it is non-invasive and relatively specific[28–30]. However, perigraft fluid may be present for up to 3 months after surgery and does not necessarily indicate infection[31,32]. Unfortunately, aspiration and culture of perigraft fluid may be positive in only 13 per cent of those with positive graft cultures after excision[20,33–36]. The indium-labelled white cell scan is the best known isotope technique for documenting the extent of infection[37,38]. Gallium or Tc^{99} hexamethyl proplene amine oxime (HMPAO) scanning require fewer facilities and produce essentially the same results in experienced hands[28,29]. A second lesson is that tests may be misinterpreted by staff who are not familiar with the problem of graft infection. Several referred patients had evidence of widespread graft infection when imaging was reviewed at this centre, yet these images were originally reported as showing no retroperitoneal involvement with infection. A final lesson relates to surgical exploration. Lack of incorporation of the graft into the surrounding tissues or extension into another anatomical compartment renders a local procedure unlikely to succeed. The authors have previously failed to appreciate this themselves, as is evident from the several cases of failure after *in situ* replacement.

What, therefore, is the role of local treatment for graft sepsis? First, most authors agree that radical graft excision is appropriate in the majority of cases and that careful case selection is required if less than radical surgery is to be attempted. *In situ* replacement was first advocated by Walker *et al.*[13] and others have also reported their experience[12,14]. These authors have suggested that this type of treatment may be appropriate in patients with 'low-grade infection' and 'sterile' perigraft fluid. Even after graft removal many studies have failed to identify an infecting organism, but his may be due to inadequate disruption of the biofilm rather than true negativity. A host *versus* graft response in culture-negative 'infection' has recently been suggested[40]. In previous reports[1,41,42] coagulase-negative *S. aureus* was the most common organism, but the pattern of bacteriology has changed[2,35,43,44]. This change may be due to the increasingly broad range of antibiotic cover used in arterial surgery or to different techniques of processing graft material for culture[33,34]. The number of aortoenteric fistulas in any series will also affect the range of bacteria encountered. Local or *in situ* procedures for 'minimally infected' or culture-negative grafts are associated with a perioperative mortality rate of 20 per cent and there remains a significant risk of recurrent sepsis. The authors question the logic of extensive surgery to perform an *in situ* replacement of a graft that will be prone to recurrent infection, when radical excision and stump closure with remote reconstruction is no more dangerous and unlikely to be affected by recurrent infection. *In situ* replacement of the aorta might be more reasonable with an antibiotic-impregnated graft[45], but the antibiotic bonding lasts only days with present techniques and long-term results are unknown[46].

In the present study, subsequent amputation was more likely with occlusive disease, a groin anastomosis and symptoms in the groin. This is because excision of a functioning graft in the groin and extra-anatomic bypass on to distal vessels, probably diseased, compromises the limb. No patient with an infected tube graft has required amputation.

Considering the data presented, the authors consider it appropriate to continue with a general policy of radical graft excision and extra-anatomic bypass for aortic prosthetic infection. Because of the association of amputation with the described triad, it may be reasonable to attempt local debridement and irrigation treatment if the graft limb is still patent, the anastomosis intact and infection in the graft localized to the groin after assessment by CT and radionuclide scanning. In the authors' experience this situation is rare; radical surgery is likely to remain the main form of treatment.

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British Journal of Surgery 1996, 83, 659–664

Inhibition of neutrophil respiratory burst and cytokine priming by γ-linolenic acid

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The effect of n-6 fatty acids, particularly γ-linolenic acid (GLA), on the oxidase response and neutrophil priming by tumour necrosis factor α and interleukin 8 was studied in both normal volunteers and patients with obstructive jaundice. GLA inhibited the neutrophil respiratory burst at concentrations higher than 50 μmmol/l, but abolished cytokine priming at concentrations as low as 1 μmmol/l. Inhibition was not the result of either cytotoxicity to the neutrophils or alteration in cytosolic free calcium homoeostasis. It is concluded that GLA is a potential inhibitor of neutrophil priming by cytokines and of the oxidative response.

The neutrophil population is of crucial importance in combating infection. There is evidence, however, that this cell population may also cause tissue damage in certain pathological situations, such as trauma[1], adult respiratory distress syndrome (ARDS)[2], sepsis[3] and rheumatoid arthritis[4]. Under these conditions neutrophils secrete hydrolytic enzymes and liberate toxic metabolites of oxygen. Neutrophil activation *in vivo* is modified by cytokines which are capable of 'priming' the neutrophil oxidative response. Known primers include tumour necrosis factor (TNF) α[5–9], interleukin (IL) 1[8,9], IL-6[10], IL-8[11], granulocyte–macrophage colony-stimulating factor[12], transforming growth factor β[13] and interferon γ[14]. There is a marked increase in serum levels of these cytokines in septic states with an accompanying increase in respiratory burst capability in the circulating neutrophils[3].

Patients with obstructive jaundice are prone to increased perioperative sepsis, and renal and wound failure. Immune malfunction, such as decreased phagocytosis, has been postulated as an important factor in this situation. Portal and systemic endotoxaemia which occur in these patients have been suggested as possible mediators for these effects. Patients with obstructive jaundice also have an overproduction of oxidative products which is related to poor clinical outcome. These patients have also been shown to have a markedly increased production of TNF-α and other cytokines from monocytes, suggesting the possibility that neutrophils in these patients may be preprimed *in vivo*[15,16].

Essential fatty acids are important for normal immune function, acting either directly or via metabolites[17]. Dietary supplementation with essential fatty acids, particularly n-3, has been reported to influence aspects of immune function, such as mononuclear cell secretory function[18,19] and neutrophil function[20]. However, n-6 fatty acids, in many ways a more important series, have not been so widely studied[21], although they are reported by several authors to possess anticancer properties. Free γ-linolenic acid (GLA) has been shown to be directly cytotoxic to malignant cells and therefore may be of some importance in tumour biology[22,23].

The effects of the n-6 fatty acid, GLA, on neutrophil respiratory burst have been investigated and inhibition of both activation and priming by TNF-α and IL-8 are reported. The inhibition of priming was apparent at low concentrations, which were not the result of cytotoxicity or inhibition of cytosolic free calcium (Ca^{2+}) signalling.

Patients and methods

Recombinant human TNF-α (National Biological Standards Board, Potters Bar, UK) 1 ng was equivalent to 50 units as assayed by the L929 bioassay[24]. Human recombinant IL-8 was also supplied by NBSB, and Fura-2-acetoxymethyl ester (Fura-2-AM) was obtained from Molecular Probes (Eugene, Oregon, USA). All fatty acids were supplied by Sigma Chemicals (Poole, UK), initially dissolved in ethanol, stored in liquid nitrogen and further diluted in Krebs medium with 0·1 per cent (w/v) bovine serum albumin for use. In this study, linoleic acid, GLA, arachidonic acid and prostaglandin (PG) E$_2$ were used.

Ethical approval for this study was given by the local ethics committee. Both control subjects and patients gave informed consent. Blood samples were taken from eight patients with obstructive jaundice (with benign ($n = 3$) or malignant ($n = 5$) biliary strictures) and ten healthy volunteers. Median (interquartile range (i.q.r.)) age for the jaundiced group was 70·5 (62–85) years: 74 (72–78) years for patients with benign strictures and 68 (62–68) years for those with malignant strictures. Median (i.q.r.) age for the age-matched control group was 68·5 (48–77) years ($P = 0·77$ *versus* jaundiced group). Median (i.q.r.) bilirubin level in patients with jaundice was 165 (40–305·5) mmol/l: 74·7 (39·0–115·0) mmol/l for patients with benign lesions and 226·0 (103·5–424) mmol/l in those with cancer. Median (i.q.r.) albumin level was 36·0 (26–45) g/l: 36 (34–45) g/l for patients with benign lesions and 33·5 (26–39·5) g/l for those with malignancy. No donors had evidence of current infection. In patients with jaundice, blood samples were taken before any clinical intervention; they were kept on ice and processed within 30 min. All subsequent procedures were carried out at 4°C. Blood was added with 25 per cent Dextran 110 (Baxter, Thefford, UK) by volume and this was allowed to sediment for 40 min. The leucocyte-rich layer was collected, laid over Ficoll-Hypaque[25] (Pharmacia, Uppsala, Sweden) and centrifugated at 1500 r.p.m. for 30 min at 4°C. The cell pellet (with polymorphonuclear cells and contaminated red cells) was treated with hypotonic lysis for 30 s to lyse red cells[26]. The cells were then resuspended and washed in HEPES (*N*-[2-hydroxyethyl] piperazine-*N*′-[2-ethanesulfonic acid]-buffered Krebs medium (NaCl 120 mmol/l, KCl 4·8 mmol/l, Mg$_2$SO$_4$ 1·2 mmol/l, K$_2$HPO$_4$ 1·2 mmol/l, CaCl$_2$ 1·3 mmol/l, HEPES 25 mmol/l, bovine serum albumin 0·1 per cent, pH 7·4). The procedure resulted in 94·2 per cent pure neutrophils (determined by Diff-Quik stain; Merz-Dade, Dudingen, Switzerland), with less than 2 per cent contamination with monocytes, as determined by non-specific esterase staining.

The neutrophil respiratory burst and its modulation by TNF-α

Presented to the Surgical Research Society in London, UK, January 1992, and published in abstract form as *Br J Surg* 1992; 79: 467
Paper accepted 20 August 1995

and IL-8 priming were monitored by luminol-dependent chemiluminescence using a purpose-built luminometer made from a photomultiplier tube (Thorn EMI 9424A; dark channel 6×10^{-3} nm per lumen, Enfield, UK). Luminometer settings were run at 970 V and discriminator at 0·3[15,27]. Neutrophils were preincubated at 37°C with either recombinant TNF-α 100 pg/ml or IL-8 100 pg/ml, with fatty acid in half the cultures for different periods, before stimulation with *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) 1 μmol/l or phorbol myristate acetate (PMA) in the presence of cytochalasin B 5 μg/ml. The concentrations and incubation period were chosen from initial time course to achieve a maximal inhibition by fatty acids and a submaximal priming[15,28]. Because of the limited life-time of neutrophils *in vitro*, cells were kept ice cold and tested immediately after incubation to 37°C; experiments were conducted within 30 min. The luminol-dependent chemiluminescence was displayed on a chart recorder and activity recorded as counts per second (c.p.s.). Luminol was used at a final concentration of 11 μmol/l.

Cytosolic free Ca^{2+} changes were measured by dual-wavelength fluorimetry of cytosolic Fura-2-AM (Spex CM; Instrument SA, Stanmore, UK) using excitation wavelengths of 340 and 380 nm and emission at 505 nm[29]. Briefly, neutrophils were incubated for 30 min at room temperature with Fura-2-AM 1·0 μmol/l, a fluorescent indicator of cytoplasmic free Ca^{2+}, which migrates into the cytoplasm during incubation. Signals were recorded at base level, after adding fatty acid to the cell suspension and after stimulation with FMLP 1·0 μmol/l. The system was calibrated using ionomycin, a calcium ionophore, at 2 μmol/l and ethylene glycol bis [β-amino ethyl ether] *N′*,*N′*,*N′*,*N′*,-tetra-acetic acid (EGTA) at 50 mmol/l.

Cell viability was measured by the trypan blue 2·5 mg/ml exclusion test and confirmed by the maintenance of low cytosolic free Ca^{2+} concentration in the resting cells and an unaltered Ca^{2+} response to stimulation with FMLP.

The Minitab computer program (Minitab, State College, Pennsylvania, USA) was used for statistical analysis. Significance was taken at $P < 0{\cdot}05$ using Student's *t* test. Data are expressed as mean(s.e.m.).

Results

Inhibition of the respiratory burst by n-6 fatty acids

Preincubation of normal neutrophils with GLA had no effect on the resting oxidase activity (i.e. before FMLP and PMA stimulation). However, it caused a significant inhibition of the FMLP- and PMA-induced respiratory burst (*Fig. 1a*). This was seen as early as 1 min after incubation with GLA and reached a maximum in approximately 10 min. At this time point, the response was significantly inhibited by GLA at 50 μmol/l (from 9697(2134) to 1417(636) c.p.s., $n = 10$, $P < 0{\cdot}05$), while lower concentrations (1–10 μmol/l) had no effect on the response (*Fig. 1b*).

This inhibition could not be accounted for by cytotoxicity, as trypan blue exclusion was not significantly decreased by concentrations of GLA of up to 100 μmol/l (*Table 1*). Furthermore, there was no significant change in the cytosolic free Ca^{2+} concentration in resting neutrophils treated with GLA (up to 100 μmol/l), nor any diminution in the transient FMLP-induced Ca^{2+} peak (*Fig. 2* and *Table 1*).

The inhibitory effects of GLA were specific to this particular fatty acid (*Table 2*), although the parent form of n-6 fatty acid, linoleic acid, was slightly inhibitory. Other lipid products such as arachidonic acid and PGE_2 had no significant effect in the same concentration range (*Table 2*). Inhibition was not limited to the FMLP-induced response, as the PMA-induced respiratory burst was also inhibited to a similar extent (*Fig. 1a*).

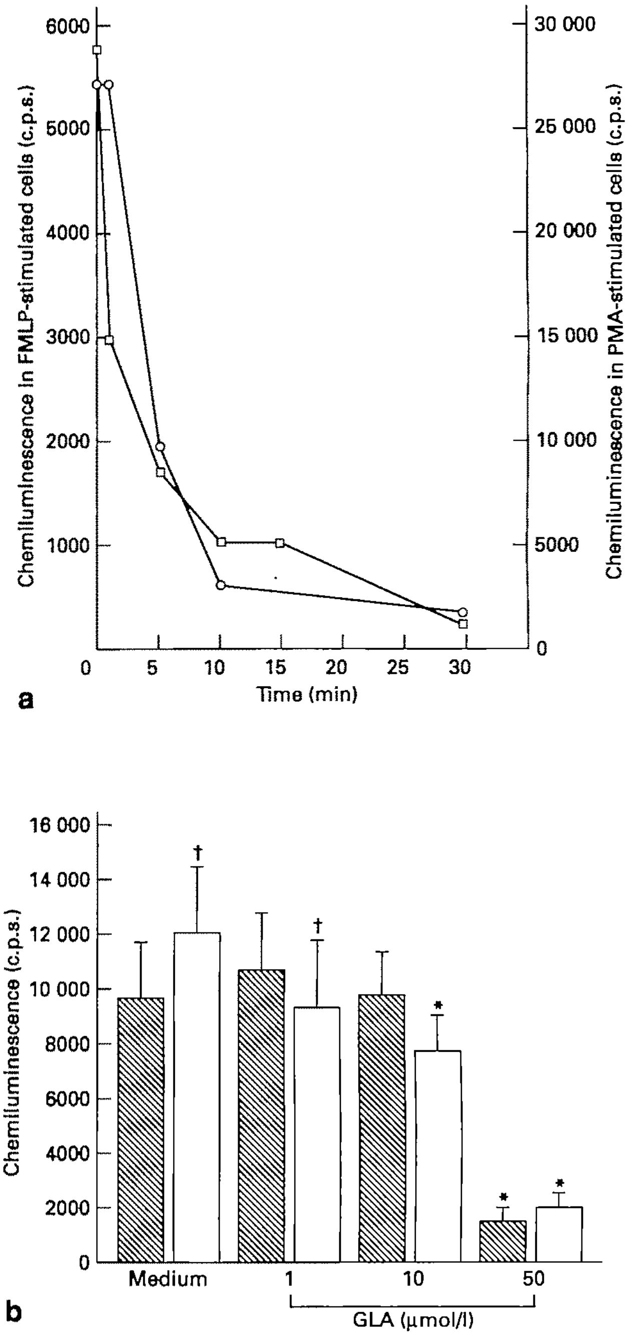

Fig. 1 Inhibition of neutrophil respiratory burst and tumour necrosis factor (TNF) priming by γ-linolenic acid (GLA). **a** Control neutrophils (5×10^6) preincubated with GLA 50 μmol/l for different periods were stimulated with either *N*-formyl-methionyl-leucyl-phenylalanine (FMLP) (□) or phorbol myristate acetate (PMA) (○). **b** Cells (5×10^6) preincubated with GLA at different concentrations with (□) or without (▨) recombinant TNF-α 100 pg/ml for 10 min and stimulated with FMLP 1 μmol/l in the presence of cytochalasin B 5 μg/ml. Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* medium control; $^\dagger P < 0{\cdot}05$ *versus* cells without TNF-α (Student's *t* test)

Inhibition of cytokine priming by fatty acids

Incubation of neutrophils with TNF-α 0·1 ng/ml for 10 min before stimulation produced an enhancement of the oxidative response to approximately 125 per cent (9697(2134) c.p.s. in the absence of TNF-α and

Table 1 Neutrophil viability after culture with γ-linolenic acid

	Cell viability with trypan blue exclusion (%)	Cytosolic calcium (nmol/l)	
		Resting neutrophils	Stimulated neutrophils
Control	93·2(0·6)	189·0(28·6)	701·3(40·0)
GLA (μmol/l)			
1	95·5(0·9)	n.d.	n.d.
10	95·0(1·8)	234·5(38·5)	814·0(71·0)
50	93·5(1·7)	167·5(42·5)	750·0(52·0)
100	92·0(1·8)	244·0(74·0)	803·5(71·5)

Values are mean(s.e.m.). GLA, γ-linolenic acid. Cells were mixed with trypan blue 2·5 mg/ml at the end of experiments and the viable cells counted. Viability was also confirmed by the resting level and *N*-formyl-methionyl-leucyl-phenylalanine-induced peak cytosolic free calcium changes. Both showed no difference between control cultures and cells with GLA up to 100 μmol/l. n.d., Not determined

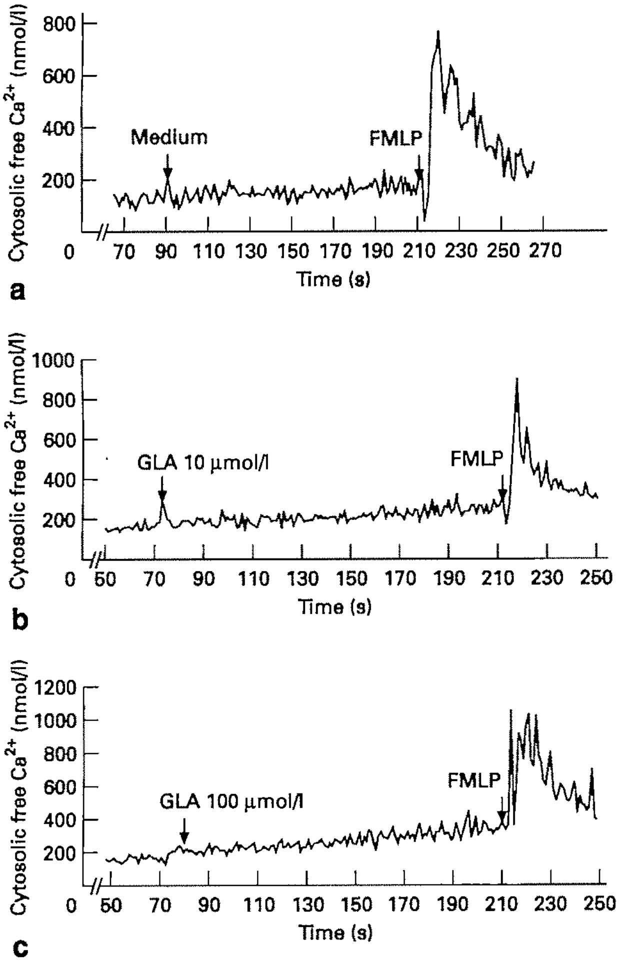

Fig. 2 Cytosolic free calcium (Ca^{2+}) concentration in neutrophils treated with γ-linolenic acid (GLA) and stimulated with *N*-formyl-methionyl-leucyl-phenylalanine (FMLP). a Baseline free Ca^{2+} concentration; b resting neutrophils treated with GLA 10 μmol/l; c resting neutrophils treated with GLA 100 μmol/l. There was no significant change in either resting level or kinetics of FMLP stimulation

Table 2 Effects of fatty acids on neutrophil respiratory burst

Fatty acid*	Respiratory burst (c.p.s.)	*P*†
None (control)	9712(252)	–
Linoleic acid	6632(1040)	0·05
γ-Linolenic acid	2315(752)	<0·01
Arachidonic acid	8191(1125)	n.s.
Prostaglandin E_2	10 555(1095)	n.s.

Values are mean(s.e.m.). *Fatty acids and prostaglandin E_2 effects at 50 μmol/l. †*Versus* control (Student's *t* test). n.s., Not significant

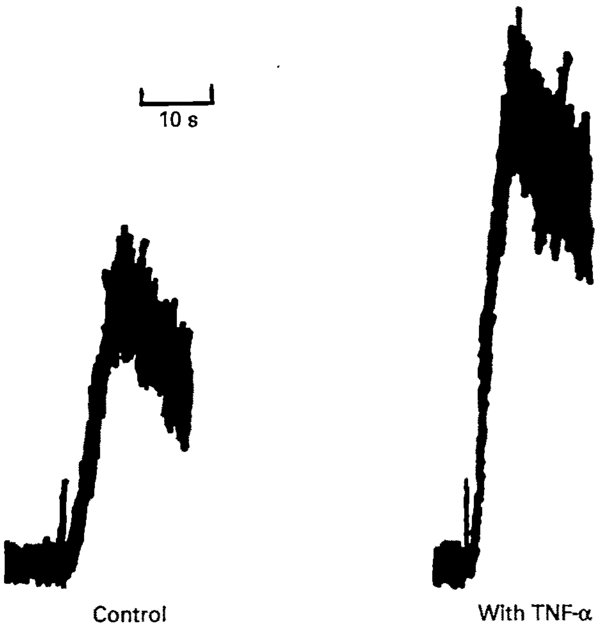

Fig. 3 Neutrophil priming by tumour necrosis factor (TNF) α. Tracing is from an experiment showing cell response to *N*-formyl-methionyl-leucyl-phenylalanine with or without TNF-α 0·1 ng/ml which, at such a concentration, will prime neutrophils

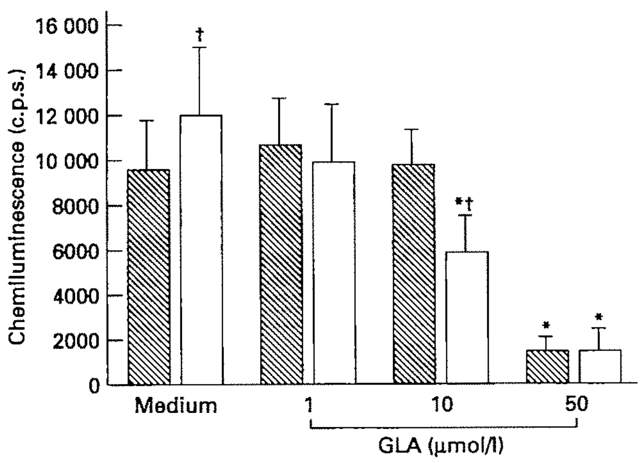

Fig. 4 Inhibition of neutrophil respiratory burst and interleukin (IL) 8 priming by γ-linolenic acid (GLA). Cells (5×10^6) were preincubated with GLA at different concentrations with (☐) or without (▨) recombinant IL-8 100 pg/ml for 10 min. Values are mean(s.e.m.). *$P < 0·05$ *versus* medium control; †$P < 0·05$ *versus* cells without IL-8 (Student's *t* test)

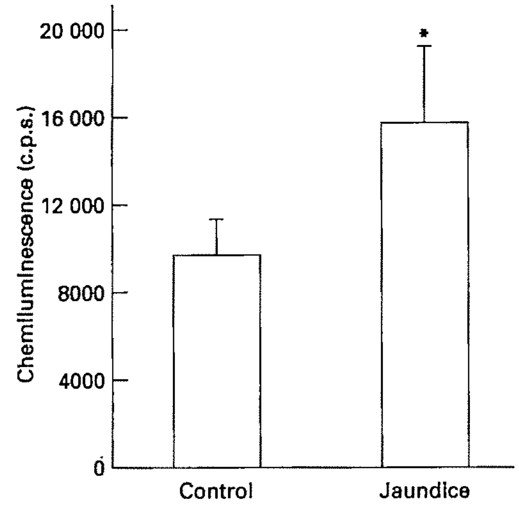

Fig. 5 Neutrophil oxidative response of controls and patients with obstructive jaundice. Values are mean(s.e.m.). $^{*}P<0{\cdot}01$ (Student's *t* test)

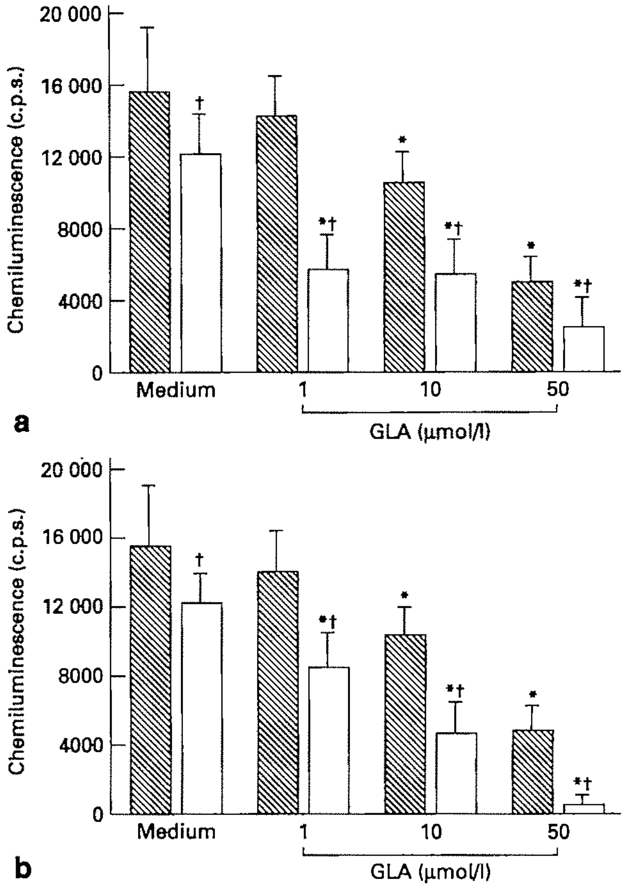

Fig. 6 Effect of γ-linolenic acid (GLA) priming by a tumour necrosis factor α or b interleukin 8 on neutrophils, from patients with obstructive jaundice. Response with (□) and without (▨) cytokine. Values are mean(s.e.m.). $^{*}P<0{\cdot}05$ *versus* medium control; $^{\dagger}P<0{\cdot}05$ *versus* cells with cytokine (Student's *t* test)

12079(2475) c.p.s. in its presence ($n=10$; $P<0{\cdot}05$) (*Figs 1b* and 3). However, when the cells were preincubated with GLA before the addition of TNF-α this priming effect of TNF-α was inhibited (*Fig. 1*). The inhibition of priming occurred at concentrations of GLA which had no direct inhibitory effect on oxidase activation. GLA 1 µmol/l abolished TNF-α priming (12079(2475) c.p.s. in the presence of TNF-α, 9366(2959) c.p.s. in the presence of both TNF-α and GLA compared with 9697(2134) c.p.s. in the absence of TNF-α). At higher concentrations of GLA (above 10 µmol/l) the direct inhibitory effect was also observed (*Fig. 1b*).

Similarly, IL-8 100 pg/ml exerted a priming effect on neutrophils to a similar extent as TNF-α[15]; this effect was also inhibited by GLA (*Fig. 4*).

Effects of γ-linolenic acid on neutrophils from patients with obstructive jaundice

As previously reported[15], neutrophils from patients with obstructive jaundice ($n=8$) showed a greatly increased level of respiratory burst compared with controls ($n=10$; $P<0{\cdot}01$) (*Fig. 5*).

When these cells were pretreated with GLA, the oxidative response was significantly reduced (*Fig. 6a*). The inhibition seen with jaundiced cells was more marked than that seen with control neutrophils (*Fig. 1*). As reported previously 'jaundiced' neutrophils were less able to be primed by cytokines and the hypothesis that they are preprimed has been proposed[15]. Priming of these cells by TNF-α and IL-8 was reduced compared with that of controls. The effect of GLA on the priming of these jaundiced neutrophils was striking. The combination of GLA and cytokines caused marked inhibition (*Fig. 6*).

Discussion

These data show that, unlike some n-3 fatty acids, the n-6 fatty acid, GLA, has an inhibitory effect on neutrophil oxidase activity. The mechanism of this inhibition was not cytotoxicity and occurred after receptor binding and the generation of the intracellular Ca^{2+} signal. Furthermore, as oxidase activation by the protein kinase C activator, PMA, was also inhibited, the possibility exists that GLA acts at a site after protein kinase C activation. A novel finding was that, unlike the n-3 fatty acids, GLA at low concentrations prevents the priming action of TNF-α and IL-8. This effect was more apparent with neutrophils from patients with obstructive jaundice, who have excessive production of oxidative products from neutrophils that appear to be preprimed *in vivo*.

There are other striking differences between n-3 and n-6 fatty acids. In contrast to the inhibitory effect of GLA, the 22–32-carbon long-chain n-3 fatty acids[18] and the n-6 fatty acid arachidonic acid[30] stimulate neutrophil chemiluminescence and the respiratory burst. However, PGE_1, a derivative of arachidonic acid, inhibits neutrophil activation[31]. This study also demonstrates that linoleic acid has a weak inhibitory effect on neutrophil activation; arachidonic acid and PGE_2 do not have a significant effect. Chain length and saturation of polyunsaturated fatty acids (PUFAs) are of critical importance in determining their biological activity. PUFAs may also have an effect on cytosolic Ca^{2+}. In a T cell line (JURKAT cells), PUFAs stimulated a rapid release of Ca^{2+} from the endoplasmic reticulum. This effect depended on the length and desaturation of the fatty acid, but not on Ca^{2+} influx or inositol lipid turnover[32–34]. The failure to detect an increase in cytosolic free Ca^{2+} concentration in response to GLA (or other PUFA) may reflect the small amount of endoplasmic reticulum in neutrophils and its low Ca^{2+} loading in circulating neutrophils[29]. Interestingly, the mechanism by which agents, such as TNF-α, induce priming does not involve cytosolic free Ca^{2+}, but is probably mediated by tyrosine phosphorylation[35,36].

The observation that priming by TNF-α and IL-8 is inhibited by GLA may have important implications. TNF-α and other cytokines are neutrophil regulators of potential clinical significance. Several authors have reported increases in circulating TNF-α and interleukin levels[3], and it is suggested that TNF-α and IL-8 are among the major cytokines responsible for neutrophil activation in disease. The authors have demonstrated previously that neutrophils from patients with obstructive jaundice have increased oxidase responses but decreased sensitivity to TNF-α and IL-8 priming[15]. These observations are consistent with *in vivo* priming by circulating TNF-α in patients with jaundice. It has therefore been proposed that inhibition of neutrophil priming may be of benefit in these critically ill patients with ARDS, sepsis, trauma, burns and some systemic diseases, such as rheumatoid arthritis, by decreasing neutrophil-induced tissue destruction[1–4]. This may have been the case in the present study for patients with obstructive jaundice. GLA has been tested on a range of normal cells *in vitro* and cytoxicity has been seen only at very high concentrations[37–40]. These findings together with other recent studies of the effects of PUFAs on neutrophil migration[41] indicate that the fatty acid might have a high therapeutic index if used clinically[42–45]. The concentrations used in this *in vitro* study can also be achieved clinically, as reported by Diboune *et al.*[46], who showed that infusion of a GLA-rich formulation raised the plasma GLA level to approximately 220 μmol/l. Finally, neutrophils from patients with jaundice showed a markedly increased burst to FMLP stimulation. This study is unable to provide further biochemical mechanisms underlying this phenomenon but the possibility exists that these cells may have a changed binding capacity to FMLP, a change seen in other diseases[47].

In summary, these studies show that the n-6 PUFA, GLA, exerts a significant inhibitory effect on neutrophil respiratory burst and in particular on cells from patients with jaundice who would otherwise have excessive secretion of oxidative products. Interestingly, GLA at much lower concentrations can also inhibit neutrophil priming by cytokines (TNFα and IL-8). GLA may therefore have a clinical role in patients with excessive neutrophil activation.

Acknowledgements

This work was supported by Scotia Pharmaceuticals and the Arthritis and Rheumatism Council (UK). Recombinant human TNF-α was a generous gift from Dr N. Matthews, Department of Microbiology, University of Wales College of Medicine, Cardiff, UK.

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British Journal of Surgery 1996, 83, 665–669

Transient rise in intact parathyroid hormone concentration after surgery for primary hyperparathyroidism

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Two-site immunometric assays for determination of the level of intact parathyroid hormone (PTH) in serum have enabled detailed clinical studies of PTH secretion. Fifty-one patients with primary hyperparathyroidism were studied before surgery and 2 years after operation. PTH levels dropped to low values after operation. A rebound increase in PTH concentration occurred from 10 days to 3 months after surgery. Abnormally raised postoperative PTH concentrations were noted in 31 per cent of the patients, who had lower serum concentrations of ionized calcium (Ca^{2+}) than the rest ($P < 0{\cdot}003$). Before operation these patients had a more pronounced hyperparathyroidism than the others. At 2 years after surgery there was still a positive correlation between PTH concentrations before and after surgery ($P < 0{\cdot}001$). The rebound increase in the level of PTH was a general phenomenon probably caused by low Ca^{2+} concentrations at the time of remineralization of bone. This phenomenon was transient. The positive correlation between preoperative and postoperative PTH concentrations shows that effects of hyperparathyroidism can remain for a long time after surgical cure.

It is now possible to determine the serum concentrations of biologically active intact parathyroid hormone (PTH) accurately by using immunometric two-site assays[1,2]. Previously available region-specific competitive radioimmunoassays measured not only intact PTH but also its metabolites. The advantages of an immunoradiometric assay have previously been reported in the diagnosis and follow-up of patients after thyroid and parathyroid surgery[3,4]. A rapid decline in PTH concentration occurs after excision of a parathyroid adenoma[1,3,5]. Using region-specific radioimmunoassays several investigators have found raised PTH concentrations after parathyroidectomy in up to 40 per cent of normocalcaemic patients[6–8]. It was not possible to determine whether this was due to a rise in intact PTH or metabolite concentrations, or whether the rise was persistent or transient.

The serum concentration of intact PTH, total calcium and ionized calcium (Ca^{2+}) was examined in patients with primary hyperparathyroidism before operation and during the 2 years after surgery with a view to determining whether the postoperative rise in PTH concentration was transient or persistent, and whether it was related to the degree of hyperparathryoidism as estimated by the preoperative PTH, calcium and Ca^{2+} concentrations. A further aim was to try to find a possible cause of the postoperative increase in the level of PTH.

Patients and methods

Patients

Fifty-one patients (46 women and five men) were operated on for primary hyperparathyroidism between September 1987 and the end of April 1989 at Sahlgrenska University Hospital, Göteborg. The mean(s.d.) age was 64·2(10·7) years. Age and sex distributions are given in *Fig. 1*. None of the patients had multiple endocrine neoplasia or any other hereditary hypercalcaemic syndrome. Three patients underwent reoperation for previously missed parathyroid adenomas. Four patients were given oral calcium supplements on the first postoperative day; the data obtained for this day were not used in the analysis.

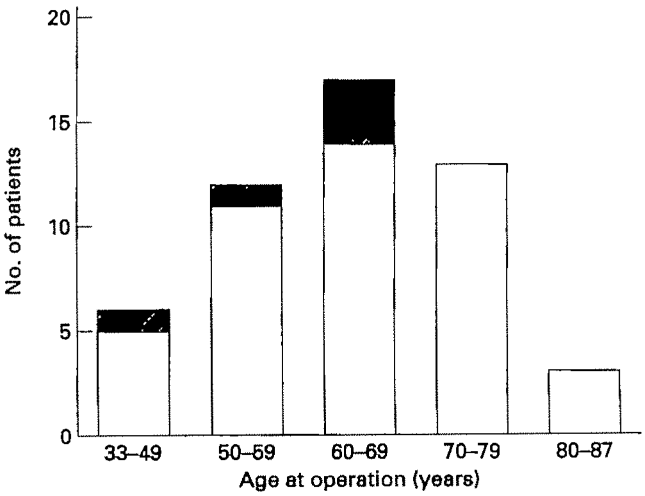

Fig. 1 Age distribution at time of surgery for primary hyperparathyroidism. □, Women; ▨, men

Surgery

Four parathyroid glands were identified in each patient but only enlarged glands were excised. Macroscopically normal parathyroid glands were not biopsied. Patients with hyperplasia of all four parathyroids underwent total parathyroidectomy and autotransplantation of part of the diseased parathyroid tissue into the abdominal subcutaneous fat tissue[9]; such patients were excluded from the study.

Blood was obtained before surgery for determination of serum concentrations of calcium, Ca^{2+}, PTH, creatinine and alkaline phosphatase. Serum concentrations of calcium, Ca^{2+} and intact PTH were obtained 1, 2 and 3 h after parathyroidectomy, and then 1, 3 and 10 days and 1, 3, 6, 9, 12 and 24 months after operation. Four patients were followed for only 12 months. The four patients who had high PTH concentrations at the completion of the study underwent further study 6–7 years after operation.

Laboratory anlaysis

Concentrations of intact PTH in fasting morning blood samples were determined by the Allegro intact PTH immunoradiometric

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Paper accepted 22 August 1995

assay (Nichols Institute Diagnostics, San Juan Capistrano, California, USA). The detection limit of this assay is 2 ng/l and the reference range 10–65 ng/l. Ca^{2+} concentration (reference range 1·18–1·31 mmol/l) was determined with a Radiometer ICA-1 instrument (Radiometer, Copenhagen, Denmark) in which samples were equilibrated at 37°C with carbon dioxide at 5·3 kPa. Values for Ca^{2+} concentrations were calculated at a pH value of 7·4.

Serum calcium levels (reference range 2·20–2·60 mmol/l) were determined by a photometric complex-binding method (*o*-cresolphthalein). Serum creatinine concentration (reference range: women 50–110 µmol/l; men 60–120 µmol/l) was determined by a modified Jaffé procedure[10]. The serum level of alkaline phosphatase (normal less than 5·0 µkat/l) was determined according to the recommendations of the Scandinavian Enzyme Committee[11].

Statistical analysis

The results are presented as mean(s.d.). Comparison between groups was made with Student's *t* test. Temporal changes within individuals were evaluated with the paired *t* test. Correlation was calculated as Pearson's coefficient of correlation.

Results

Histopathological examination of excised parathyroid glands showed adenoma in 45 patients and multiple parathyroid gland disease in six. The six patients with multiple gland disease had two or three enlarged parathyroids which were excised, normal looking parathyroids being left *in situ*.

Serum creatinine concentrations and alkaline phosphatase activity

The mean(s.d.) preoperative serum creatinine concentration was 86(16) µmol/l. Three patients had raised concentrations of 130, 138 and 142 µmol/l. No correlation was found between preoperative or postoperative PTH levels and serum creatinine concentrations. The mean(s.d.) serum alkaline phosphatase activity was 4·0(1·3) µkat/l, and nine patients had increased levels. No correlation was found between preoperative alkaline phosphatase activity and PTH concentrations.

Parathyroid hormone, calcium and Ca^{2+} levels

Before operation all patients were hypercalcaemic. The mean(s.d.) calcium, Ca^{2+} and PTH concentrations were 2·84(0·15) mmol/l, 1·47(0·09) mmol/l and 100(49) ng/l respectively. Thirteen patients (25 per cent) had PTH concentrations in the high normal range, but these levels were inappropriately high for the simultaneously high serum calcium levels. All other patients had raised PTH concentrations. Significant correlations were observed between PTH and serum calcium and Ca^{2+} levels ($r = 0·59$ and 0·71, $P < 0·001$). The mean(s.d.) preoperative serum calcium, Ca^{2+} and PTH concentrations in the six patients with multiple gland disease were 2·83(0·12) mmol/l, 1·48(0·08) mmol/l and 107(68) ng/l respectively.

Postoperative PTH concentrations fell rapidly in each patient. The lowest PTH values were recorded within the first 3 h after adenoma excision. The mean(s.d.) nadir PTH concentration was 7·5(5·1) ng/l. The Ca^{2+} concentration at this time was 1·33(0·08) mmol/l. On the first postoperative day the mean serum Ca^{2+} concentration was subnormal and PTH concentrations had risen to normal values in two-thirds of patients. On the third postoperative day the PTH level was within the normal range in all patients, but half had hypocalcaemia. At day 10, five patients had mild hypocalcaemia. All patients were normocalcaemic 1 month after surgery and remained so for the duration of the study.

At 12 months following operation the mean(s.d.) calcium, Ca^{2+} and PTH concentrations were 2·31(0·11) mmol/l, 1·24(0·04) mmol/l and 39(18) ng/l respectively; at 24 months they were 2·34(0·08) mmol/l, 1·25(0·03) mmo/l and 36(17) ng/l. Four patients had raised PTH values with normal serum calcium levels at both 12 and 24 months after surgery. One of these (patient no. 30) had

Table 1 Clinical details of four patients with persistently high serum parathyroid hormone levels

Patient no.	Postop. time at which PTH level first raised	Age at last check (years)	Observation time (years)	Creatinine (µmol/l)* Preop.	Creatinine (µmol/l)* Last check	Comment
2	1 month	79	7	68	80	Hypercalcaemic for 6 years before cure of hyperparathyroidism
14	10 days	89	6	92	136	
30	12 months	80	7	100	132	
38	10 days	79	6	83	87	Carcinoid syndrome

*Reference range 50–110 µmol/l. PTH, serum intact parathyroid hormone

Table 2 Levels of parathyroid hormone and Ca^{2+} in four patients with persistently raised parathyroid hormone values

	Before surgery		2 years postop.		At check-up		After extra calcium	
Patient no.	PTH (ng/l)	Ca^{2+} (mmol/l)	PTH (ng/l)	Ca^{2+} (mmol/l)	PTH (ng/l)	Ca^{2+} (mmol/l)	PTH (ng/l)	Ca^{2+} (mmol/l)
2	243	1·65	81	—	78	1·22	67	1·18
14	257	1·58	75	1·23	120	1·21	Not treated (89 years old)	
30	118	1·48	81	1·18	120	1·19	70	1·26
38	168	1·46	103	1·23	410	1·02	330	1·18

PTH, serum intact parathyroid hormone. Reference ranges: PTH, 10–65 ng/l; Ca^{2+}, 1·18–1·31 mmol/l been operated on for multiglandular parathyroid disease (*Tables 1* and *2*). Some 24 months after parathyroidectomy the mean(s.d.) serum calcium, Ca^{2+} and PTH levels for the six patients with multiglandular parathyroid disease were 2·33(0·07) mmol/l, 1·24(0·04) mmol/l and 43(20) ng/l respectively.

Following the postoperative decline, a rebound increase in PTH concentration occurred in all patients (*Fig. 2*). In 86 per cent of patients the highest postoperative PTH concentration was found between 10 days and 3 months after operation. The highest postoperative PTH concentrations were found in 16 women, who were significantly older than the other patients (mean(s.d.) 69(12) *versus* 62(9) years, $P<0\cdot05$). Four of these patients had higher postoperative than preoperative values. Those with raised PTH concentrations had lower Ca^{2+} concentrations at the time of their highest PTH value than had the other patients (mean(s.d.) 1·22(0·02) *versus* 1·26(0·03) mmol/l, $P<0\cdot003$). Patients with raised PTH levels after surgery had higher preoperative PTH ($P<0\cdot001$), calcium ($P<0\cdot02$) and Ca^{2+} ($P<0\cdot05$) concentrations than the rest, indicating that before surgery they had more severe hyperparathyroidism.

Following the exclusion of those with raised PTH concentrations from the analysis, the 35 patients with the highest postoperative PTH levels within the normal range still had a higher concentration 10 days ($P<0\cdot02$), 1 month ($P<0\cdot001$) and 3 months ($P<0\cdot0005$) after surgery than they had at 12 and 24 months.

At 3 h after surgery the Pearson correlation for PTH *versus* Ca^{2+} concentration changed from significantly positive to negative. The correlation continued to be negative at all the subsequent postoperative time-points (*Fig. 3*), but was not statistically significant.

The Pearson correlation for preoperative *versus* postoperative PTH values was positive at all time-points except the day after surgery. At day 10 after surgery, and at all subsequent time-points, the correlation was highly significant ($P\leq0\cdot003$) (*Fig. 4*).

Some 2 years after parathyroidectomy four patients still had a raised serum PTH concentration. These patients were re-evaluated 6–7 years after surgery (*Tables 1* and *2*) and the serum PTH level was still high. Two of these patients had impaired renal function as shown by increased serum creatinine values. Before operation one patient had the second highest PTH and Ca^{2+} values in the series and had had proven hypercalcaemia for 6 years before surgery. Another patient had carcinoid syndrome and a short bowel resulting in severe diarrhoea. The latter patient had hypocalcaemia and the others had normal Ca^{2+} concentrations. Three of these patients underwent a 1-month trial with oral calcium carbonate at a daily dose of 0·75–1·0 g Ca^{2+}. The patient with carcinoid syndrome also received 0·5 μg alfacalcidol daily. The PTH values dropped by 14–42 per cent and these patients have continued this treatment.

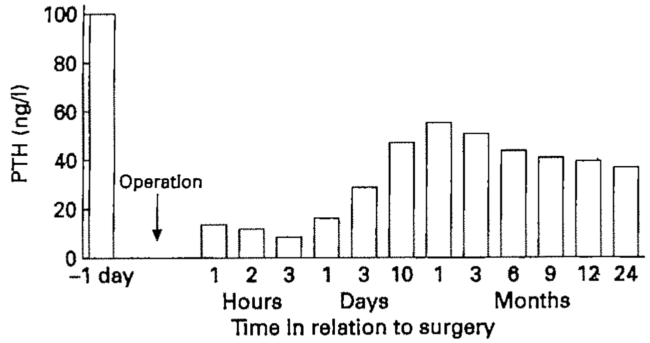

Fig. 2 Mean serum intact parathyroid hormone (PTH) concentrations before and after surgery. Note the rebound phenomenon. The reference range is 10–65 ng/l

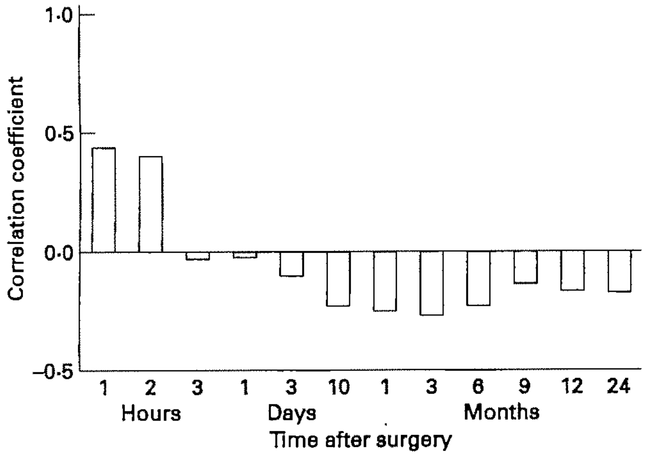

Fig. 3 Pearson correlation for postoperative serum parathyroid hormone and ionized calcium concentrations. The negative correlations found 3 h after surgery and at the subsequent time-points were not significant. The largest negative correlation coefficient was found 3 months after operation ($r=0\cdot27$, $P=0\cdot06$)

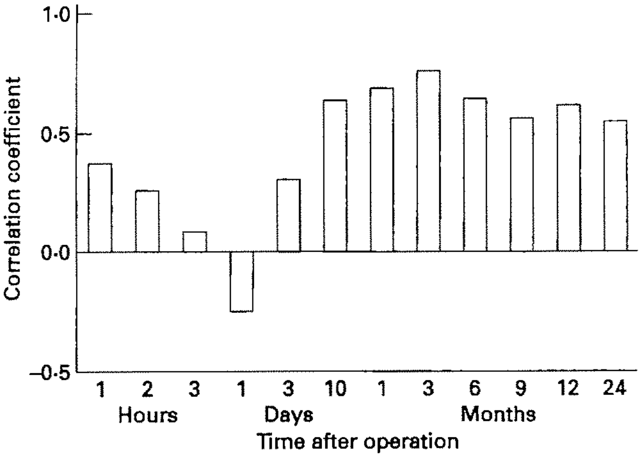

Fig. 4 Pearson correlation for preoperative *versus* postoperative serum parathyroid hormone concentrations. Except for the day after surgery, there were positive correlations at all postoperative time-points

Discussion

Parathyroid function was examined before and after excision of parathyroid adenoma in patients with primary hyperparathyroidism, using a sensitive two-site immunoradiometric assay specific for intact biologically active PTH(1–84). Unlike at some centres[5,12], the authors seldom give calcium supplementation during the postoperative period. This facilitated the present study of postoperative changes in PTH and calcium concentrations.

During the first few hours after surgery a pronounced decline occurred in serum PTH concentration, while the level of Ca^{2+} was still raised. The lowest mean serum Ca^{2+} level was found 20 h after surgery. At that time, the serum PTH concentration started to rise as a decline in serum Ca^{2+} concentration stimulated PTH secretion[13]. At 10 days after surgery five patients had mild hypocalcaemia, but 1 month after operation all patients were normocalcaemic and remained so for the rest of the study.

In most patients a rebound increase in serum PTH concentration occurred 10 days to 3 months after surgery. Serum PTH concentrations during this period were significantly higher than those recorded subsequently, showing that the rebound rise in PTH concentration was transient. In previous studies raised PTH concentrations have been observed after operation in up to 40 per cent of normocalcaemic patients operated on for primary hyperparathyroidism[6–8]. In these studies, only the postoperative rise above the reference range was discussed. The present study demonstrated a significant transient rise in PTH concentration also in patients with normal serum PTH levels after surgery. This observation shows that a rebound rise in serum PTH concentration is a general phenomenon after surgery for hyperparathyroidism. Sixteen patients (31 per cent) had the highest postoperative PTH values above reference values. Their PTH concentrations were twice the level seen in the other patients but they had significantly lower serum Ca^{2+} levels. Before operation these patients had higher PTH and Ca^{2+} concentrations, indicating that they had more severe hyperparathyroidism than the rest, which could have led to greater depletion of bone mass. The patients with raised PTH concentrations after surgery had two other characteristics related to bone loss: they were all women and were older than the other patients. Remineralization of the skeleton occurs after surgery for primary hyperparathyroidism, but decreases sharply with time. The remineralization is incomplete and only a poor gain of bone mineral can be expected after 1 year[14], although recent studies by Silverberg *et al.*[15] documented that the increase occurs for at least 4 years. According to Abugassa and co-workers the bone mass increases by approximately 10 per cent within 3 months after successful parathyroid surgery and then remains stable during the first postoperative year. This increase in bone mass after parathyroid surgery[16] is synchronous with the rebound rise in PTH concentration found in the present study. This suggests that the main cause of the transient postoperative rebound increase in PTH secretion results from a decrease in serum Ca^{2+} concentration due to increased deposition of calcium in bone. This theory is supported by the finding of lower Ca^{2+} concentrations in patients with postoperative PTH concentrations above the normal range.

At 2 years after surgery four patients still had raised PTH concentrations, and 6–7 years after parathyroid surgery one of these had hypocalcaemia, probably due to malabsorption because she had carcinoid syndrome and short bowel syndrome with diarrhoea. Two patients with raised serum creatinine values probably had secondary hyperparathyroidism due to renal dysfunction. There was no obvious explanation in the fourth patient, who had a mild increase in PTH level. However, her hyperparathyroidism had been severe and of long duration before surgery. Three of these patients had short-term trials of calcium carbonate treatment. The patient with hypocalcaemia also received alfacalcidol. PTH levels dropped by 14–42 per cent, supporting the assumption that the rise in PTH values in these cases was compensatory in response to lack of calcium.

When the four patients with persistently high PTH values were excluded, the mean PTH concentration 2 years after surgery was 33 (95 per cent confidence interval (c.i.) 30–36) ng/l. This concentration is similar to that of 32 (95 per cent c.i. 14–60) ng/l found by Sokoll and co-workers[17] when using the same PTH assay in 245 healthy postmenopausal women. This comparison suggests a normalization of PTH levels in patients in the present series.

After exclusion of the four patients with persistently high PTH values, a significantly positive correlation was still found between preoperative PTH concentration and that obtained 2 years after surgery ($r = 0{\cdot}41$, $P = 0{\cdot}006$). There is no obvious explanation for this remaining link to hyperparathyroidism.

This study has shown that after parathyroidectomy for adenoma postoperative increases in PTH concentration can occur in patients who are normocalcaemic, as previously reported by Duh *et al.*[7] and others[6,8]. These rises are transient and do not indicate recurrent disease. The rebound phenomenon is a general one, occurring also in patients with postoperative PTH levels within the normal range. If the postoperative increases in the level of PTH are long lasting, the presence of secondary hyperparathyroidism should be considered.

Acknowledgements

This work was supported by grants (6534) from the Swedish Research Council.

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British Journal of Surgery 1996, 83, 670–671

Surgical workshop

Use of a laparoscopic trocar for percutaneous introduction of drains into intra-abdominal abscesses

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Drainage of an intra-abdominal abscess is a difficult problem. Laparotomy with open drainage, although effective, carries a certain morbidity and mortality rate. Percutaneous drainage using one of the various pigtail catheters is often ineffective, especially when there is debris within the abscess. These catheters tend to become blocked unless they are flushed regularly owing to a smaller lumen[1]. A method is described for introducing a wide-bore Robinson drain under ultrasonographic guidance using local anaesthesia.

Surgical technique

Patient 1

A 57-year-old man developed an interloop abscess after a triple bypass operation for carcinoma of the head of the pancreas. An ultrasonographic scan showed the abscess to be bilocular with communicating components within the pelvis and the lower abdomen, and extending up to the anterior abdominal wall. A 5-mm disposable laparoscopic trocar and cannula (AutoSuture, Ascot, UK) was introduced into the upper component through a small stab incision in the skin and advanced until the tip lay within the abscess cavity as visualized on ultrasonography (*Fig. 1*). The trocar was pulled out and a 16-Fr Robinson drain passed down the cannula (*Fig. 2*). A subsequent ultrasonographic scan showed that the cavities had collapsed. The drain was removed after 5 days and the patient made an uneventful recovery.

Patient 2

A 23-year-old woman had a laparoscopic colectomy with terminal ileostomy for intractable Crohn's colitis. After operation she developed abdominal pain, pyrexia and leucocytosis. Abdominal ultrasonography showed a large amount of free fluid within the peritoneal cavity, which was purulent on aspiration and was thought to be infected blood within the peritoneal cavity. A 16-Fr Robinson drain was passed into the peritoneal cavity through a 5-mm laparoscopic trocar as previously described, and 500 ml of fluid drained. An ultrasonographic examination after 48 h revealed little residual fluid, and the patient made an uneventful recovery.

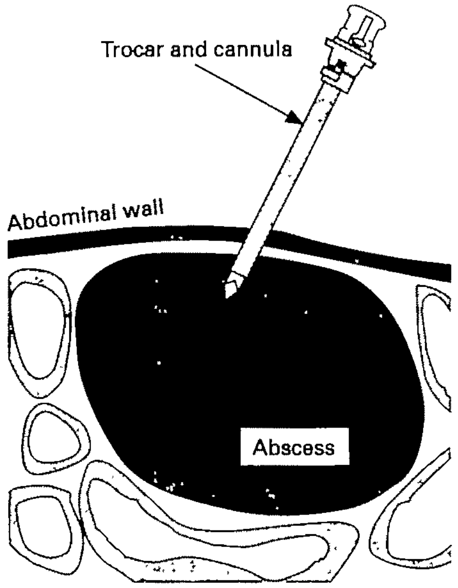

Fig. 1 Laparoscopic trocar and cannula advanced into the abscess

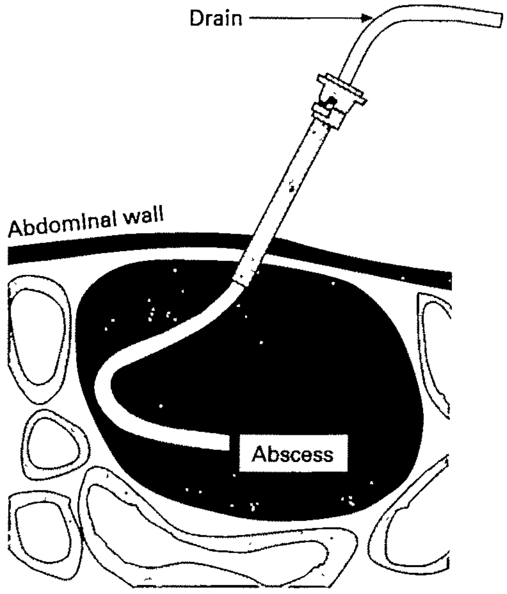

Fig. 2 Drain introduced into the abscess through the laparoscopic cannula

Discussion

The use of percutaneous drains for the drainage of intra-abdominal collections is well described[2,3]. Although associated with a lower morbidity rate, they are sometimes less effective than open surgical drainage partly because of the smaller diameter of drains that can be inserted by this means. Various techniques have been described to introduce drains of larger diameter by the percutaneous route, most of which rely on initial tract dilatation using serial fascial dilators. This manoeuvre is relatively time consuming compared with the technique described here.

A laparoscopic trocar and cannula has been used to drain hydatid cysts of the liver under direct vision at laparotomy with good results[4]. This technique has now been extended to the drainage of intra-abdominal

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Paper accepted 23 August 1995

abscesses. If there is considerable distance between the abdominal wall and the underlying viscera deep to the abscess (as confirmed on ultrasonographic scan), it is considered that the introduction of a disposable cannula with a rapid tip withdrawal is a safe and effective way to drain intra-abdominal abscesses.

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British Journal of Surgery 1996, 83, 672–674

Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer

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The poor prognosis of patients with gastric cancer with free abdominal tumour cells on cytological examination has been described in Japan. In a randomized trial in the Netherlands comparing D_1 and D_2 lymphadenectomy for gastric cancer, patients were subjected to cytological examination of abdominal washings on an optional basis; findings were of no consequence for scheduled treatment. Cytology results in 535 patients were obtained, in 457 (85·4 per cent) after curative resection and in 78 (14·6 per cent) after palliative operation. There was a clear association of positive cytology results with serosal invasion (12 per cent positive cytology) and lymph node infiltration (7·5 per cent positive cytology). Survival of those with positive cytology results was significantly lower than that of those with negative findings, irrespective of the procedure employed (curative or palliative). Cytological examination of abdominal washings increases the accuracy of staging and improves the selection of patients suitable for curative or palliative resection.

The prognosis of gastric cancer is related to the extent of local tumour growth and the presence of lymph node, peritoneal or hepatic metastases. Free cancer cells might induce or indicate early peritoneal seeding with subsequent peritoneal metastasis. Whether a positive cytology result from abdominal washings implicates a poor prognosis has not been systematically studied in Western patients and the therapeutic consequences remain unclear. The prognostic significance of the results of cytological examination of abdominal washings was therefore investigated in the Dutch Gastric Cancer Trial.

Patients and methods

The Dutch Gastric Cancer Trial is a randomized controlled trial comparing limited (D_1) with extended (D_2) lymph node dissection for gastric cancer, conducted from 1989 until 1993 in the Netherlands[1]. Patients with histologically confirmed adenocarcinoma of the stomach and without clinical evidence of metastasis were randomized for D_1 or D_2 lymph node dissection and underwent laparotomy. Cytology was an optional investigation and without consequences for the scheduled treatment. Cytological examination was carried out before handling the tumour. The abdominal cavity was washed with 100 ml normal saline and at least 50 ml, aspirated from the pouch of Douglas, was centrifuged. The cell layer was stained with Papanicolaou and Giemsa. The material was classified as 'negative' (no free abdominal tumour cells), 'positive' (tumour cells present) or 'suspected' (tumour cells suspected, but not conclusive). When assessment was not possible due to lysis of cells or contamination with blood this was recorded as 'no judgement'.

Of the 996 eligible patients, curative resection (complete tumour removal, no metastasis) was possible in 711. The remaining 285 patients had non-curative operations (evidence of remnant tumour or metastasis). Patients having curative surgery had the allocated D_1 or D_2 dissection and the others had a palliative operation considered appropriate by the surgeon.

The results of cytological examination were retrieved from the trial forms and pathological records in 535 patients (53·7 per cent), 457 having curative and 78 non-curative resections.

Survival was calculated with the Kaplan-Meier method and survival curves were compared with the Gehan–Wilcoxon test. Six patients were lost to follow-up directly after leaving the hospital and were censored at 30 days. Multivariate logistic regression analysis was done to identify prognostic variables for a positive cytology result. All statistical analyses were performed with the SPSS/PC+ 4.0 program (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics are listed in *Table 1*. In 468 patients (87·5 per cent) no free cancer cells were detected, although in ten the presence of malignant cells was suspected. In 38 patients (7·1 per cent) free abdominal tumour cells were demonstrated. In 19 patients no judgement could be given. The incidence of positive cytology results was highest in patients having non-curative surgery (18 (23 per cent) of 78), but free abdominal tumour cells were detected in 20 (4·4 per cent) of the 457 undergoing curative resection. For patients undergoing curative resection, there was no difference in distribution of the results of cytology in those having D_1 or D_2 dissection.

Table 2 shows that a positive cytology finding is strongly associated with serosal invasion and *Table 3* demonstrates that in the absence of lymph node involvement only two patients (0·9 per cent) had a positive cytology result, whereas 18 (7·5 per cent) patients with positive lymph nodes had free abdominal tumour cells. The predictive value of a positive cytology result for serosal invasion and positive lymph nodes was high: of the 20 patients with positive cytology, 19 had suspected or definite serosal invasion and 18 had lymph node involvement.

When serosal invasion was detected, a positive cytology result had a relative risk of 11 compared with that in patients without serosal invasion ($P = 0·03$). Lymph node involvement gave a fivefold increased chance of a positive cytology result compared with that in patients without node involvement, but this was, like pTNM (tumour node metastasis) stages III and IV (compared with stages I and II) and T_4 stage (compared with T_{1-3} stage), a non-significant effect in addition to serosal invasion (*Table 4*).

Fig. 1 shows the survival of patients undergoing 'curative' surgery. The few patients with suspected cytology or no judgement had a similar survival to those

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Table 1 Characteristics of 535 patients with gastric cancer undergoing cytological investigation of abdominal washings

	Curative	Non-curative
No. of patients	457	78
Sex ratio (M:F)	262:195	53:25
Age (years)		
<60	155 (33·9)	24 (31)
60–70	162 (35·4)	28 (36)
>70	140 (30·6)	26 (33)
Randomization		
D_1	244 (53·4)	32 (41)
D_2	213 (46·6)	46 (59)
Cytology outcome		
Negative	418 (91·5)	50 (64)
Suspected	6 (1·3)	4 (5)
Positive	20 (4·4)	18 (23)
No judgement	13 (2·8)	6 (8)

Values in parentheses are percentages

Table 2 Cytology findings and clinical serosal invasion in 457 patients undergoing curative surgery

Cytology outcome	No invasion	Suspected invasion	Definite invasion
Negative	208 (95·9)	123 (89·8)	81 (84)
Suspected	2 (0·9)	2 (1·5)	2 (2)
Positive	1 (0·5)	7 (5·1)	12 (12)
No judgement	6 (2·8)	5 (3·6)	2 (2)
Total*	217 (100)	137 (100)	97 (100)

Values in parentheses are percentages. *Clinical serosal invasion was not assessed in six patients with negative cytology results

Table 3 Cytology and lymph node involvement in 457 patients undergoing curative surgery

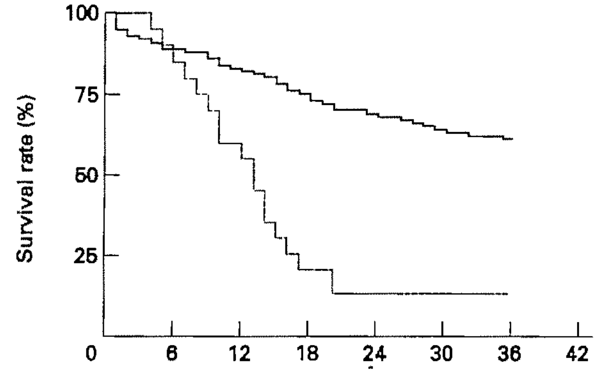
	Lymph node involvement	
Cytology outcome	Negative	Positive
Negative	204 (94·9)	213 (88·4)
Suspected	1 (0·5)	5 (2·1)
Positive	2 (0·9)	18 (7·5)
No judgement	8 (3·7)	5 (2·1)
Total*	215 (100)	241 (100)

Values in parentheses are percentages. *Lymph node involvement was not assessed in one patient with negative cytology findings

Table 4 Multivariate assessment of risk factors for positive cytology results in curatively resected gastric cancer

Risk factor	Relative risk	*P*
Serosal invasion	11·3 (1·3–100·5)	0·03
Lymph node involvement	4·8 (0·5–52·2)	n.s.
pTNM stage > III	1·2 (0·1–16·1)	n.s.
T_4 stage	0·6 (0·2–2·1)	n.s.

Values in parentheses are 95 per cent confidence intervals. TNM, tumour node metastasis; n.s., not significant.



No. at risk				
Negative cytology	437	345	225	133
Positive cytology	20	12	2	1

Fig. 1 Survival in 457 patients with gastric cancer after curative surgery according to negative (——) and positive (-----) cytology findings. $P < 0·001$ (Gehan–Wilcoxon test)

with a negative cytology result and are therefore included in this group. For patients having curative surgery a positive cytology result was found to be a bad prognostic factor, with a median survival of 1·1 year ($P = 0·0001$). For patients undergoing non-curative surgery, detection of free tumour cells was a bad prognostic sign, superimposed on their poor prognosis; none of these patients survived more than 1 year.

Discussion

The outcome of cytological examination of abdominal washings is not routinely used in the assessment of curability of cancer in the Western world. Japanese investigators have demonstrated that, in a small proportion of patients deemed to have been treated curatively, cytological examination reveals free abdominal tumour cells and these patients had a considerably worse prognosis than those without such free cells[2,3]. Nakajima *et al.*[2] found a positive cytology result in 16 per cent of patients undergoing macroscopic curative resection and in 47 per cent of those having non-curative operations. Boku *et al.*[3] detected a positive result in 34·8 per cent of those with macroscopic serosal invasion, but free tumour cells were absent in patients in whom the serosa was not involved. In the present study the rate of positive cytology was 4·4 per cent in patients having curative resection and 23 per cent in those undergoing non-curative surgery. There was a strong relationship between positive cytology findings and serosal invasion and lymph node involvement; only one patient (0·5 per cent) without serosal invasion had a positive cytology result, whereas free abdominal tumour cells were found in 12 per cent of those with tumours invading the serosa. The incidence of positive cytology was lower in the present series than in the aforementioned Japanese studies, but cytological investigation was optional and inexperience with fixation methods and interpretation of results may have reduced the detection rate. This is suggested from the high number of missing and inconclusive (suspected or no judgement) results.

For patients undergoing curative and non-curative resection, a positive cytology result was a significant prognostic factor for survival (*Fig. 1*). This is in accordance with the Japanese experience and suggests that the procedure should be routine in the investigation of patients with gastric cancer.

The therapeutic consequences of a positive cytology result are less certain, however. In general, survival after surgery for gastric cancer is not significantly improved by adjuvant chemotherapy[4]. Peritoneal deposits and free abdominal cancer cells are not amenable to surgery or radiotherapy. Nakajima *et al.*[2] treated patients with a positive cytology finding with intraperitoneal mitomycin, but an influence on survival could not reliably be extracted from their data. The study of Hagiwara *et al.*[5] showed a significant survival improvement for cytology-positive patients treated with mitomycin adsorbed on carbon particles. This result needs to be confirmed and is currently being examined in a randomized British trial.

Acknowledgements

Cooperative investigators: Reference surgeons: P. van Elk, St Geertruiden Hospital, Deventer; D.J. Gouma, H. Obertop and C.W. Taat, Academic Medical Centre, Amsterdam; S. Meyer, Free University Hospital, Amsterdam; J. Plukker, University Hospital, Groningen; H. Tilanus, University Hospital, Rotterdam; K. Welvaart, University Hospital, Leiden; M. Sasako, National Cancer Center Hospital, Tokyo, Japan. Reference pathologists: G.J. Fleuren and J.A. Bruijn, University Hospital, Leiden; J.W. Arends, University Hospital, Maastricht; A.L.N. Grond, Regional Pathology Laboratory, Leeuwarden; J. van de Stadt, Regional Pathology Laboratory, Enschede, The Netherlands.

The cooperation of the 80 participating surgeons and 45 participating pathologists of the Dutch Gastric Cancer Group is gratefully acknowledged.

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British Journal of Surgery 1996, 83, 675–678

No obvious advantages for thoracoscopic two-stage oesophagectomy

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Thoracoscopically assisted Ivor–Lewis oesophagectomy potentially combines the pulmonary advantages of transhiatal oesophageal dissection, with the visibility and control permitted by thoracotomy. This study reviewed 17 patients who underwent this procedure with an intrathoracic anastomosis. Five patients required conversion to thoracotomy, four because of technical difficulties with the anastomosis. After operation 13 patients had radiological evidence of atelectasis, six developed a left pleural effusion and five had clinically significant pneumonia. Three patients developed an anastomotic leak, two of whom died giving an in-hospital mortality rate of 12 per cent. Median postoperative hospital stay was 12 days. Four patients developed benign anastomotic strictures requiring dilatation. The 1- and 2-year survival rates were 73 per cent (11 of 15 patients) and 63 per cent (five of eight) respectively. The use of minimal access techniques in this context does not appear to reduce the postoperative incidence of either pulmonary or anastomotic complications.

Surgical excision offers the best chance of long-term survival and effective palliation for patients with oesophageal carcinoma[1,2]. However, the complications, particularly pulmonary, from surgery that involves both upper abdominal laparotomy and thoracotomy are substantial[3,4]; they have proved difficult to predict, and preoperative clinical assessment is relied upon heavily[5,6].

Transhiatal oesophagectomy with a cervical anastomosis and avoiding thoracotomy appears to reduce the incidence of major pulmonary complications[7,8]. However, the complications of blind dissection of the thoracic oesophagus make overall advantages difficult to demonstrate[9–11] even under maximal direct vision[12] or with accompanying mediastinoscopy[9,13] or laparoscopy[14].

With the advent of video-assisted minimally invasive surgery, thoracoscopic mobilization of the oesophagus with anastomosis either in the chest[15,16] as in this series, or as a third stage in the neck[17–25], seemed to offer the ideal solution, allowing accurate dissection and haemostasis in the chest without thoracotomy and its associated morbidity.

Despite early enthusiasm[17,21,22] more recent reports have suggested that the expected benefits have not been seen, and patients have continued to suffer the pulmonary complications previously attributed to thoracotomy[9,20,23–26].

This study reviewed retrospectively 17 patients who underwent thoracoscopic oesophagectomy with laparotomy, with particular reference to the pulmonary and other complications of the procedure.

Patients and methods

Median (range) age of the patients (ten men, seven women) was 61 (42–73) years. Sixteen patients presented with dysphagia and one with reflux; they described a median (range) weight loss of 5 (0–21) kg. At endoscopy the upper limit of the tumour from the incisors ranged from 30 to 40 cm. In the 12 tumours traversed by the endoscope, the length ranged from 2 to 7 cm. Biopsy showed eight adenocarcinomas and nine squamous cell carcinomas. Preoperative ultrasonography and computed tomography (CT) in each patient identified no liver metastases or lymphadenopathy; the tumour was imaged by CT in 13 patients.

No patient had pre-existing renal or hepatic disease, but three patients had significant lung disease, two cardiovascular disease and one was diabetic. Twelve patients did not smoke and nine did not drink alcohol. Preoperative investigation of pulmonary function showed a median (range) arterial partial pressure of oxygen of 95·6 (65·2–105·8) mmHg, arterial partial pressure of carbon dioxide of 35·3 (29·3–43·5) mmHg, percentage of predicted forced vital capacity (FVC) of 91 (69–121) per cent, percentage of predicted forced expiratory volume in 1 s (FEV) of 91·5 (69–99) per cent and percentage of predicted FEV/FVC ratio of 100·5 (76–109) per cent. Serum albumin, haemoglobin and white cell count were all within the normal range. Three patients were assessed as being in American Society of Anesthesiologists (ASA) grade I, 11 were assessed as grade II and three were grade III.

The modifications of the Ivor–Lewis procedure have been described previously[15]. Following the initial laparotomy to mobilize the stomach, a right thoracoscopic approach was used to mobilize the oesophagus. The head of a circular stapling gun was withdrawn through a small oesophagotomy into the oesophagus above the tumour and after transection of the oesophagus above the oesophagotomy with a linear staple gun, a double-staple technique was used to perform the intrathoracic anastomosis. Complications and deaths that occurred before discharge from hospital were recorded.

Results

At operation there were three mid-oesophageal, seven lower oesophageal and seven gastro-oesophageal tumours with 12 of the tumours being palpable at the level of the diaphragm on initial laparotomy. In addition, six patients had palpably involved lymph nodes at this level. Five unsealed Thoracoports (Auto Suture, Ascot, UK) were used in 15 patients; two required an additional port for lung retraction to avoid a capnothorax with its associated problems[23]. The azygos vein was divided using a linear endoscopic vascular stapler (GIA 30, Auto Suture) in ten patients. The intrathoracic anastomosis was performed using a 25-mm ($n = 13$) or 28-mm ($n = 2$) circular stapling gun (Auto Suture CEEA), or 25-mm curved intraluminal stapler ($n = 2$) (Ethicon Endo-Surgery, Edinburgh, UK). In five patients the procedure was converted to open operation using a small thoracotomy, in four because of technical failure of the anastomosis and in one because of inability to ventilate on one lung; the latter patient

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Paper accepted 6 December 1995

required a second thoracotomy the same evening for bleeding. Other operative complications included opening the left pleura in one patient, and splenectomy was required in two. A median (range) of 2 (0–7) units of blood was given at operation. Median (range) anaesthetic time was 330 (230–450) min, and the duration of single-lung ventilation 135 (90–240) min.

After operation the patients were all ventilated for a median (range) of 24 h (4 h–49 days); six patients had a thoracic epidural for 24–48 h. Median (range) time spent in the intensive therapy unit (ITU) was 1 (1–56) day. Postoperative complications are listed in *Table 1.* All patients had at least two chest radiographs in the first 3 days after operation and atelectasis was assessed radiographically in each patient. The pleural effusions recorded all required either aspiration or drainage; the right chest was routinely drained via an underwater seal, but there was a significant incidence of effusions in the left chest. There were three postoperative anastomotic leaks which caused an empyema in one patient and both hospital deaths. The deaths occurred 20 and 70 days after operation, and involved two of the last three patients in the series. Median (range) postoperative hospital stay was 12 (9–70) days.

Histological examination of the resected specimen confirmed nine as adenocarcinomas and eight as squamous cell carcinomas. Resection margins were clear in 15 patients; the two patients with involved margins died 11 and 5 months after operation from tumour recurrence. In 14 specimens, tumour invasion of the perioesophageal tissues was seen, with involvement of the muscularis propria in the other three cases. A median (range) of 7 (2–18) lymph nodes were identified; lymphatic involvement in 13 patients led to four tumours being classified as Tumour Node Metastasis (TNM) stage IIA, one as IIB and 12 as stage III.

Anastomotic stricture occurred in seven patients (four benign and three malignant). Patients with malignant strictures were all intubated for palliation, and the four with benign strictures required a total of 14 endoscopic dilatations. Two of the patients whose surgery was converted to open operation required referral for control of thoracotomy wound pain.

Since surgery a median (range) 23 (7–35) months ago, seven patients have died, four with tumour recurrence, and one further patient has recurrent tumour. Median (range) postoperative survival to date is 17 months (20 days–31 months). Eleven of 15 patients survived the first year and five of eight the second.

Table 1 Complications arising in hospital, showing the incidence in the group as a whole and those occurring in the five patients whose procedure was converted to thoracotomy

Complication	No. ($n = 17$)	Converted ($n = 5$)
Transient air leak	1 (6)	0
Perioperative aspiration	0 (0)	0
Clinically significant pneumonia	5 (29)	2
Atelectasis	13 (76)	
Right	6	0
Left	3	0
Both	4	2
Effusion	8 (47)	
Right	2	2
Left	6	0
Empyema	1 (6)	1
Anastomotic leak	3 (18)	1
Death in hospital	2 (12)	1

Values in parentheses are percentages

Discussion

Compared with the transhiatal approach there is no doubt that thoracoscopic visualization allows enhanced tumour and nodal clearance, with minimal blood loss, and avoids damage to surrounding tissues. Avoidance of a thoracotomy seems likely to abolish such complications as post-thoracotomy pain, scapular fixation and frozen shoulder.

However, to perform the procedure required two experienced laparoscopic surgeons. The operating time was longer than that for the open procedure, and a prolonged period of single-lung anaesthesia was required in some patients.

In the past 10 years this unit has performed 146 oesophageal resections of which 85 were Ivor–Lewis procedures with the intrathoracic anastomosis being performed by hand in 29 cases and stapled in 56. Clinically significant respiratory complications occurred in 24 patients (30 per cent). Pleural effusions requiring drainage occurred on the left in ten patients and on the right in a further three (15 per cent), and there were ten anastomotic leaks (12 per cent). Median (range) duration of stay in the ITU was 2 (0–21) days and postoperative hospital stay 14 (8–68) days. The mortality rate in hospital was 10 per cent.

By comparison, in the present series there was a high incidence of technical problems encountered with the intrathoracic anastomosis, with four patients requiring conversion to open surgery as a result. The rate of anastomotic leakage was 18 per cent, similar to the 12 per cent leakage rate that would be expected following conventional resection[4], as this difference represents only one patient in this small series.

There are several technical difficulties with thoracoscopic anastomosis, including the untested double-stapling technique for oesophageal anastomoses, an inevitable small amount of spillage of oesophageal contents during the process of withdrawing the staple gun anvil into the oesophagus, and difficulty in docking the detached anvil into the circular stapling gun and assessing the tension of the tissues during this process. The fact that this series represents a learning curve for the authors is also almost certainly relevant and detracts from the value of any direct comparison with the results of open surgery in this or other units.

The postoperative stricture rate was also high, which reduced the effectiveness of the procedure in terms of palliation of dysphagia. The indirect access to the oesophagus contributed to the fact that a small 25-mm staple gun was used in the majority of cases which probably increased the stricture rate. Creation of the anastomosis in the neck would have shortened the thoracoscopic operating time, and may have reduced the significance of anastomotic leaks both in terms of conversion and mortality rates.

The incidence of pulmonary complications based on radiological criteria in this series is higher than the rate of 32–56 per cent after conventional surgery[5,6,27]. The thoracotomy wound itself is only one of many factors involved in the high incidence of postoperative pulmonary complications after oesophagogastrectomy and this probably explains the disappointing lack of impact of thoracoscopic surgery.

Other factors which contribute to pulmonary complications include an upper abdominal incision which has been shown to reduce FVC and arterial oxygenation for several days after uncomplicated surgery[28,29], probably as a result of wound pain and abdominal distension altering respiratory mechanics[29]. Second, prolonged periods of single-lung ventilation are likely to have contributed to pulmonary complications. It has been known for many years that inadequate lung expansion in the collapsed lung results in atelectasis and the development of substantial ventilation–perfusion mismatching and shunting. In addition, a prolonged period of single-lung anaesthesia during thoracoscopy has been shown to exacerbate both absorption atelectasis and transudation of fluid in the dependent ventilated lung[30], while alveolar overdistension may contribute to ventilator-induced pulmonary oedema and acute lung injury, progressing in some patients to respiratory failure[31,32]. The prone position described by Mitchell *et al.*[18] may have certain advantages by allowing continued partial ventilation of the lung which in their small series reduced the incidence of pulmonary complications.

Other contributory factors may include malnutrition[33], the presence of the stomach in the right chest acting as a 'hydropneumothorax'[34], a diminished cough reflex due to damage to branches of the vagal nerve and diaphragm[35] and perioperative pulmonary aspiration. Trauma, inflammation or endotoxins from the gut have all been shown to release mediators that can directly injure the lung[36].

The extent of tumour resection thoracoscopically appeared to be adequate oncologically. Early submucosal spread of malignant cells longitudinally away from macroscopic tumour margins has resulted in positive resection margins in 12–35 per cent of oesophagogastrectomies[27]. The early death from recurrence of two patients in this series confirms it as a major risk factor[27]. The advantages of lymph node clearance for oesophageal carcinoma remain the subject of debate, with individual authors able to show a survival advantage in selected tumours[37,38]. The similarity in survival after transhiatal oesophagectomy has led many to question the role of such extensive surgery[4] and the thoracoscopic procedure conforms well with current practice in terms of the lymphadenectomy possible.

The 12 per cent operative mortality rate is similar to the mean of 13 per cent reported over the past 15 years[4], and the 1- and 2-year survival rates were high considering the relatively advanced stage of the tumours.

The duration of postoperative hospitalization is similar to that for conventional Ivor–Lewis oesophagectomy in this unit and to the 10–21 days reported in the literature for transhiatal oesophagectomy[11,12]. No subjective assessment of subsequent quality of life has been performed, and this could be one important advantage of minimal access surgery, which for most patients remains a palliative procedure.

While this study represents the authors' learning curve for this technically challenging procedure, it emphasizes the need for critical assessment of the application of minimal access techniques. This study suggests that attempts to reproduce the Ivor–Lewis oesophagectomy thoracoscopically are feasible, but do not appear to reduce the postoperative incidence of either pulmonary or anastomotic complications.

Acknowledgements

The authors acknowledge the significant contribution of the anaesthetists involved, particularly Dr C. Hanning.

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British Journal of Surgery 1996, 83, 679–707

Surgical Research Society Abstracts

The following abstracts were presented at the 83rd meeting of the Surgical Research Society, with Professor Sir D. C. Carter in the Chair. The meeting was organized by the Nuffield Department of Surgery, University of Oxford, and held on 4–5 January 1996 in the University of Oxford. Ninety-seven papers were presented during the scientific sessions, which were preceded by a Symposium on the Management of Abdominal Aortic Aneurysms. The Patey Prize was awarded to Mr A. K. Kakkar for his paper entitled 'Tissue factor expression modulates pancreatic cancer cell invasion'.

Identification and characterization of novel ion channels present in the pancreatic beta-cells of neonates with nesidioblastosis

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Nesidioblastosis represents a heterogeneous group of conditions characterized by an increased basal glucose requirement and inappropriately high plasma insulin concentration in the presence of hypoglycaemia. The aim of this study was to investigate the subcellular mechanisms responsible for insulin secretion under these conditions. Five neonates with nesidioblastosis underwent 95 per cent pancreatectomy after failing to respond to medical treatment. Using a combination of collagenase digestion and mechanical dissociation, islets of Langerhans were isolated from the operative specimens. Patch clamp techniques were used to study the properties of the ion channels. Experiments were carried out using the cell-attached patch and excised inside-out patch configurations. In normal human insulin-secreting cells, K$^+$ adenosine 5′-triphosphate (ATP) channels dominate beta-cell electrophysiology. These channels are open in intact cells and are responsible along with the Na$^+$–K$^+$ ATPase for establishing the high resting negative membrane potential. Glucose-induced closure of these channels initiates depolarization of the membrane, leading to the opening of voltage-gated Ca^{2+} channels. The subsequent appearance of action potentials due to Ca^{2+} influx is responsible for an increase in Ca^{2+} concentration and the initiation of insulin secretion.

In both the cell-attached ($n = 41$) and excised inside-out ($n = 60$) patch clamp recordings from the nesidioblastosis cells functional K$^+$ ATP channels were absent. This caused the beta-cells to be spontaneously depolarized, resulting in mean resting Ca^{2+} levels more than twofold higher than those found in normoglycaemic human beta-cells. Several novel and previously undescribed channels were also observed. These included a low conductance K$^+$ channel with a linear current–voltage relationship that was activated by both diazoxide ($n = 8$) and somatostatin ($n = 6$), and a nucleotide-regulated K$^+$ selective channel.

It has been demonstrated for the first time that K$^+$ ATP channels are absent in the beta-cells of neonates with nesidioblastosis, resulting in subversion of the stimulus–secretion coupling events. These findings are a major consideration in our understanding of the cellular pathophysiology of nesidioblastosis.

Increased intestinal permeability and altered mucosal immunity in patients with jaundice

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Endotoxaemia and bacterial translocation may underlie the high incidence of septic complications in the patient with jaundice. The degree of mucosal immunity may also contribute. This study examined the effect of obstructive jaundice on intestinal permeability and immunological cellular infiltration.

Eighteen patients were studied, 11 with jaundice and seven age-matched hospitalized controls. Gut permeability was measured by the lactulose/mannitol absorption test. Exposure to endotoxin was determined by measuring antiendotoxin core immunoglobulin G (IgG) antibodies (EndoCAb) with an enzyme-linked immunosorbent assay. Endoscopic biopsies of the second part of the duodenum were evaluated for morphology and CD3 (T cell), CD68 (macrophage) and major histocompatibility complex (MHC) class II antigens were detected immunohistochemically.

	Controls	Patients with jaundice
Bilirubin (μmol l^{-1})	7 (5–18)	294 (199–499)*
Lactulose : mannitol ratio	0·01 (0·01–0·04)	0·3 (0·14–0·52)*
IgG EndoCAb (MI ml^{-1})	152 (37–196)	248 (115–325)*

Values are median (interquartile range). *$P < 0{\cdot}05$ *versus* controls (Mann–Whitney U test)

Immunohistochemistry showed substantial mucosal macrophage infiltration and increased expression of MHC class II antigens on CD3-positive cells in the patients with jaundice. There was no difference in gut mucosal morphology between groups.

There was a 30-fold increase in gut permeability in patients with jaundice compared with controls, with associated evidence of chronic systemic endotoxaemia. In addition, there was evidence of immunological activation at the gut mucosal level in the patients with jaundice. These data show intestinal barrier function to be impaired in patients with jaundice. This may underlie the high risk of sepsis in these patients.

Application of neural networks to prognostication in colorectal cancer

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The prediction of survival after surgery for colorectal cancer is unreliable. Even the best of the pathological staging techniques, such as Dukes, are only able to give percentage survival figures relating to the population as a whole over set periods of time. Expert systems and artificial intelligence programmes have previously been unable to provide a consistently superior performance. Neural networks, which are able to 'learn' from established outcome data, represent an alternative form of artificial intelligence. Emulating a biological system's computational techniques facilitates a level of flexibility and accuracy of pattern recognition impossible to achieve with conventional systems.

The ability of neural networks to prognosticate for individual patients following surgery for colorectal cancer was investigated. Unselected 5-year follow-up data on 334 patients with colorectal cancer were used to teach and validate the networks. Several network designs were constructed: 41 input parameters made up the first layer of neurones, 12–15 neurones were utilized in the middle layer with the output neurone providing a yes/no answer. The networks achieved an accuracy of greater than 80 per cent for the prediction of cause-specific mortality from colorectal cancer at 9, 12, 15, 18, 21 and 24 months. These results far exceeded the ability of traditional Dukes staging to predict survival. The networks were able to accurately predict, in 3-month periods, the duration of survival of individual patients and not just the population group to which they belonged.

As they are provided with more data and 'learn' more about the disease, the accuracy of the networks' predictions will increase still further. It is concluded that this technology may soon allow accurate individual prognostication in colorectal cancer.

Inhibition of endotoxin and nuclear factor kappa B mobilization prevents thoracoabdominal aortic aneurysm repair-associated neutrophil activation

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It has recently been shown that polymorphonuclear neutrophils (PMNs) are activated during visceral reperfusion in thoracoabdominal aortic aneurysm (TAAA) repair and that activation is associated with the development of systemic complications after operation. It has also been shown that plasma endotoxin antibody levels fall during this operation, suggesting that endotoxin may be absorbed from the ischaemic gut lumen. Endotoxin may therefore be involved in PMN activation during TAAA repair. Endotoxin-mediated PMN activation occurs via mobilization of cytoplasmic nuclear factor kappa B (NFκB).

The role of endotoxin and NFκB in PMN activation during TAAA surgery was studied. Venous blood samples were taken before operation and at 10-min intervals during the operation in 21 patients undergoing TAAA repair (five type II, four type III and 12 type IV). PMN surface CD11b expression and nuclear NFκB were measured by flow cytometry and plasma endotoxin absorption was measured by chromogenic Limulus Amoebocyte Lysate assay.

There was a positive correlation between intraoperative plasma endotoxin absorption and PMN CDllb expression ($r = 0{\cdot}8283$, $P = 0{\cdot}001$). The ability of preoperative and intraoperative plasma samples to activate control PMNs was assessed in a whole blood co-culture assay. Endotoxin was inhibited by addition of polymyxin B 50 mg l^{-1} to the co-culture and NFκB mobilization by the addition of pyrrolidine dithiocarbamate (PDTC) 1 mmol l^{-1}. The *Table* shows baseline (preoperative plasma) and peak PMN stimulation by plasma from blood samples taken during TAAA repair.

	Plasma only	
	Baseline	Peak
CD11b	63(32)	159(47)*
NFκB	103(16)	216(23)*
	Plasma + polymyxin B	
	Baseline	Peak
CD11b	72(42)	103(43)†
NFκB	n.a.	n.a.
	Plasma + PDTC	
	Baseline	Peak
CD11b	22(10)	23(12)†
NFκB	42(6)	37(14)†

Values are mean(s.e.m.) mean channel fluorescence. n.a., Data not available. $^*P<0{\cdot}05$ peak *versus* baseline; $^\dagger P<0{\cdot}05$ plasma stimulated: inhibitor *versus* no inhibitor (Student's *t* test)

These results show that endotoxin is associated with PMN activation during TAAA repair. Furthermore, *in vitro* endotoxin inhibition results in a significant but not complete reduction in PMN CDllb expression. In contrast, NFκB inhibition abrogates the PMN CDllb response completely. NFκB may be a novel target for prevention of PMN activation during TAAA repair.

Effect of cisapride on colonic smooth muscle in idiopathic slow transit constipation

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Evidence exists that cisapride exerts a prokinetic action on the colon of individuals with constipation of diverse aetiologies. However, little is known with regard to its effect in patients with the more specific entity of idiopathic slow transit constipation (ISTC). The influence of cisapride on agonist-induced responses was investigated in human colonic smooth muscle, with the aim of characterizing its effects on normal tissue and that from patients with ISTC.

Biopsies of sigmoid colon (1 cm^2) were taken from the fresh specimens of six patients undergoing resection for colorectal carcinoma and four patients for ISTC. Isometric tension was recorded from circular muscle strips approximately 5 mm × 1 mm mounted horizontally in a perfused tissue bath. After a period of equilibration the perfusate was sequentially changed to include increasing doses of carbachol (300 nmol–100 μmol). After a further equilibration period, the experiment was repeated with cisapride 400 nmol added to all solutions.

Cumulative concentrations of carbachol produced a dose-dependent oscillatory rise in tension of the muscle strips. The EC_{50} of peak tension in the control tissue was 3·50 ± 0·63 μmol compared with 1·81 ± 0·52 μmol in the ISTC group, increasing to 3·90 ± 0·49 μmol and 2·82 ± 0·57 μmol respectively in the presence of cisapride. A dose-dependent increase in the frequency of oscillations was observed in both groups, which persisted in controls in the presence of cisapride. In the ISTC group, however, low-dose agonist (100 nmol) in the presence of cisapride induced near maximal frequency responses.

The circular muscle from patients with ISTC showed a greater sensitivity to cholinergic stimulation than control tissue. Cisapride 400 nmol produced a reduction in the sensitivity of the muscle to cholinergic stimulation, especially in the ISTC group. Cisapride appeared to have a selective effect on the frequency of contractile oscillations in muscle from patients with ISTC. These data show differences in the response of the circular muscle of patients with ISTC and controls to cisapride, which may be unmasking an abnormality in ISTC most likely at the level of surface membrane electrical events.

Early results of endovascular abdominal aortic aneurysm repair

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Transfemoral endovascular abdominal aortic aneurysm repair was carried out in 44 patients with a median age of 68·5 (interquartile range (i.q.r.) 62–77) years and aneurysm diameter 6 (i.q.r. 5·4–6·6) cm. Twenty-four of the patients were considered to be high risk and unsuitable for conventional surgery and 16 of these were referred by other centres.

Preoperative assessment included spiral computed tomography (CT) using multiplanar reconstruction and calibrated aortography. Modified Gianturco stent (Cook), Verisoft Dacron graft (Meadox Medicals) and Wallstent (Schneider) were used. The procedure was performed in the operating theatre under general anaesthesia. An aorto-uni-iliac graft was used in 29 patients, bifurcated in 13 patients and aorto-aortic in two patients. Emergency repair for leaking aneurysms was successfully performed in two patients.

Endovascular repair was successfully performed in 38 of 44 patients and four required exposure of the aneurysm and placement of external ligatures to achieve a seal around the proximal stent. In another two patients inaccurate deployment necessitated removal of the endoprosthesis and replacement with a conventional graft. Successful endovascular procedures had a median duration of 160 (i.q.r. 120–210) min with a median operative blood loss of 500 (i.q.r. 500–550) ml; all of these patients were mobile and resumed normal diet within 48 h. Following elective repair the mortality rate within 30 days was three of 42 (7 per cent). All deaths occurred in the high-risk group after open intervention. At a median follow-up of 6·5 (i.q.r. 2–11) months, 40 of 44 patients remain alive and well. The graft remains in satisfactory position in all cases. In three patients there remains localized flow of contrast through the aneurysm sac on CT.

Early results indicate that endovascular aneurysm repair is associated with rapid recovery and a low morbidity and mortality rate. It is less traumatic and the majority of patients who are deemed unfit for open surgery can safely undergo endovascular repair. However, at this stage there remains a 10 per cent conversion rate and a similar risk of death for this group.

Electrically stimulated smooth muscle sphincter

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Electrically stimulated striated muscle neosphincters are used for faecal incontinence. There have been no reported studies on electrical stimulation of smooth muscle to produce a sphincteric effect. The feasibility of developing an electrically stimulated smooth muscle neosphincter was assessed.

Experiments were performed on rabbits anaesthetized with 25 per cent urethane. At laparotomy, a pressure probe (Gaeltec) was introduced into the lumen of the distal colon. Electrical stimulation was performed via intramural stainless steel wire electrodes using a Grass SD9 constant voltage DC stimulator.

Basal colonic pressure was 4–13 (median 11) cmH$_2$O. Spontaneous contractions occurred at the rate of 3–4 per 10 min with peak pressures of 9–25 (median 17) cmH$_2$O. On electrical stimulation, contractions occurred after a latent period of 12–18 (median 16) s. Peak pressures were achieved in 24–80 (median 40) s. With pulse duration of 1ms, no contractions were observed with a voltage below 10 V (8 mA). Peak pressures greater than 25 cmH$_2$O were produced by a minimum of 10 V (8 mA). Peak pressures with stimulated contractions were significantly higher than those with spontaneous contractions: with stimulation of 10 V, 1 ms at 10 Hz, the peak pressures were 14–37 (median 26·5) cmH$_2$O ($n = 10$, $P = 0{\cdot}01$, Mann–Whitney *U* test). During continuous stimulation (300 s), the contractions lasted from 45 to 96 (median 74) s. Intermittent stimulation using trains of electrical pulses of 1–2-min duration at 1–2-min intervals produced repeated contractions throughout the experiment, which lasted for 6 h. Monophasic current produced contractions with significantly higher peak pressures than biphasic current (33–59 (median 44) *versus* 21–49 (median 33) cmH$_2$O; $n = 10$, $P < 0{\cdot}002$, Mann–Whitney *U* test). Two bands of contractions were produced when electrical stimulation was performed with two pairs of electrodes more than 2·5 cm apart.

A sphincteric effect with intraluminal pressures of more than 25 cmH$_2$O can be achieved by electrical stimulation of rabbit colon. Electrical stimulation of smooth muscle has a potential application in patients with faecal incontinence either alone or as an adjunct to a striated muscle neosphincter.

Regulation of myeloperoxidase activity in an *in vitro* model of systemic inflammatory response syndrome

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Neutrophil (PMN) myeloperoxidase (MPO) activity plays a central role in the modulation of reduced nicotinamide adenine dinucleotide (phosphate) (NAD(P)H)-dependent respiratory burst activity through the formation of hypochlorous acid (HOCl). Taurine acts as an antioxidant through the formation of taurine chloramine from HOCl. However, little is known regarding the regulation of MPO by the inflammatory mediators endotoxin (LPS) and tumour necrosis factor (TNF) and, in particular, the effect of taurine on the activity of this enzyme in the presence of these mediators. This study evaluated the role of the inflammatory mediators LPS and TNF on MPO activation and assessed the effects of taurine on this interaction.

To assess the effects of LPS and TNF on taurine transport into PMNs, cells (2×10^6 ml^{-1}) were incubated with LPS 20 μg, TNF 3 ng or LPS/TNF (20 μg/3, 6, 9 ng) for 1 h followed by addition of [^{3}H]taurine. Incorporated [^{3}H]taurine was counted and related to μg protein per incubation. The effects of LPS and TNF on the PMN respiratory burst were assessed by flow cytometry. LPS and TNF were cultured with MPO 25 microunits for 2 h at 37°C to evaluate their direct effects on enzyme activation in the absence or presence of taurine 0·75μmol l^{-1} using the O-dianisidine method.

Neither LPS, TNF nor their combination altered taurine transport in PMNs. Both LPS and TNF significantly upregulated the PMN respiratory burst ($P < 0{\cdot}05$). TNF upregulated MPO activity from mean(s.d.) 100(7·2) to 153(2·3) per cent ($P = 0{\cdot}01$) but this effect was attenuated in the presence of taurine (112·7(1·7) per cent). LPS had no direct effect on PMN MPO activity.

Both LPS and TNF enhanced respiratory burst activity, but only TNF upregulated MPO which may enhance HOCl-mediated tissue damage. Increased MPO activity was abrogated by the antioxidant taurine. When human PMNs were stimulated with TNF the upregulation of MPO activity was not associated with the anticipated uptake of taurine. Thus transport of the antioxidant taurine into PMNs may be significantly altered during systemic inflammatory response syndrome (SIRS) by TNF and/or other cytokines. These data suggest that the potential for neutrophil-mediated tissue damage during SIRS may be enhanced and that this may be attenuated with supplementary taurine.

Leucocyte infiltration and aneurysm pathogenesis: matrix metalloproteinase-induced matrix degradation

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Abdominal aortic aneurysms are characterized by degradation of the extracellular matrix (ECM), induction of endogenous matrix metalloproteinases (MMPs) and development of a chronic inflammatory infiltrate. At the present time it is unclear whether the leucocyte response is a primary aetiological event or secondary to medial elastolysis. This study was designed to investigate the role of white cell infiltration on proteolysis within the ECM.

It has previously been demonstrated that pretreatment of arterial organ cultures with pancreatic elastase results in matrix degradation and induction of MMPs. In this study 1-cm^2 segments of porcine aorta ($n = 7$), preincubated with elastase 100 units ml^{-1}, were co-cultured for 48 h with $3{\cdot}5 \times 10^7$ autologous leucocytes before incubation in tissue culture for 11 days (leucocyte co-cultures). Paired samples were cultured identically in the absence of leucocytes (control cultures), and the two groups were compared with respect to the degree of ECM degradation and MMP production.

Leucocyte co-cultures developed a widespread inflammatory infiltrate after 3 days of culture. Stereological analysis revealed that both culture groups demonstrated a time-dependent depletion of elastin ($P < 0{\cdot}001$, Kruskal–Wallis test) but that elastolysis was more marked in the leucocyte co-cultures ($P < 0{\cdot}001$, Mann–Whitney U test). Gelatin gel enzymography demonstrated production of MMPs (55–250 kDa) within the tissues that was significantly higher in the leucocyte co-cultures than in controls ($P < 0{\cdot}05$, Mann–Whitney U test). The presence of MMP-1, -2, -3 and -9 was determined in both groups by immunoblotting, and the active isomer of MMP-9 was identified uniquely in the leucocyte co-cultures.

These data suggest that leucocytes may accelerate vascular ECM degradation by secreting activated MMPs. This finding may partially explain the association between aneurysm pathogenesis and white cell infiltration.

In vivo leucocyte emigration and locomotion in tissue in response to experimental venous hypertension

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Leucocyte trapping and activation in the microcirculation of the lower limbs may play an important role in the aetiology of skin damage in venous disease. Leucocyte emigration from the microcirculation and subsequent locomotion in response to venous hypertension was studied in a group of 12 normal volunteers. Two 0·5-cm^2 dermal abrasions were made with a dental stone over the gaiter area of the leg and the flexor aspect of the forearm (control) which were covered with moist micropore membranes. Volunteers lay supine for 30 min, then stood supported for 30 min to raise venous pressure in the leg, and finally lay supine again for 30 min. The experiment was repeated in six volunteers lying supine for the whole period. The membranes were changed and collected every 15 min, fixed in formal saline, and dual stained for monocytes and polymorphonuclear leucocytes. The type of cell emigration and the furthest distance travelled (leading front) by the cells through the membrane were measured.

	Lying (basal)	Standing	Lying
Leg	75 (68·1–79·4)	72·3 (65·0–76·7)	58·7 (54·4–69·4)*
Arm	85 (67·2–93·7)	84 (67·0–89·3)	82·8 (76·8–95·7)

Values are median (interquartile range) distance travelled. $^*P = 0{\cdot}012$ *versus* standing (Wilcoxon matched pairs signed rank test)

In the 30 min following venous hypertension white blood cell migration in the leg showed a significant fall, but there was no significant change in the arm, or when the experiment was repeated with the volunteers lying supine for the entire period (data not shown).

Leucocyte migration is decreased immediately following experimental venous hypertension possibly because of release of factors inhibiting migration.

Objective assessment of skin changes in venous disease using a tissue tonometer

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No objective method is currently available for assessing the skin changes of chronic venous insufficiency. A skin tonometer has been devised to compare skin compliance in patients with venous disease with that in control subjects. Fifty-four patients with venous disease confirmed by duplex ultrasonography and 12 controls were studied. Patients were assigned to one of three clinical groups (Hawaii classification): C_3 – oedema, C_{4a} – pigmentation alone and C_{4b} – lipodermatosclerosis (LDS). A 4-mm diameter plunger was applied to the skin 5 cm proximal to the medial malleolus or over the most severe region of skin change, and loaded with a 30-g weight. The movement of the plunger was measured for 5 min using a linear variable differential transformer position detector. The initial displacement of the plunger (within 1 s) reflects the compliance of the skin. The slower subsequent movement was assessed by fitting two exponential regression lines (1–10 s, 100–300 s), for which both the time constant and amplitude were calculated by a computer.

Patient group	Initial displacement 0–1 s (mm)	Indentation 1–10 s (mm)
Control ($n = 12$)	2·43 (2·30–2·85)	0·27 (0·21–0·38)
LDS ($n = 34$)	0·79 (0·67–1·14)*	0·42 (0·24–0·77)†
Pigment ($n = 9$)	2·41 (2·24–3·23)	0·80 (0·48–0·89)‡
Oedema ($n = 11$)	2·31 (1·45–3·02)	0·62 (0·51–0·77)§

Values are median (interquartile range). $^*P < 0{\cdot}0005$ *versus* control (initial displacement); $^\dagger P = 0{\cdot}016$, $^\ddagger P = 0{\cdot}013$, $^\S P = 0{\cdot}0074$ *versus* control (indentation) (Mann–Whitney U test)

In patients with LDS skin compliance is substantially reduced compared with that in control subjects or those with pigmentation without LDS. Skin tonometry provides an objective means of assessing skin changes in patients with chronic venous insufficiency.

Chronic venous ulceration: comparison of duplex assessment of venous reflux in the affected and non-affected legs

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Venous reflux is generally accepted as the primary cause of chronic venous ulceration, although the relative importance of reflux at different sites remains unclear. The aim of this study was to compare the patterns of venous reflux in ulcerated and unaffected legs.

Fifty-four patients with chronic venous ulceration of one leg and no history of ulceration in the contralateral leg underwent duplex ultrasonography, performed by one consultant radiologist. There was no significant difference between ulcerated and non-ulcerated legs in the pattern of either deep or superficial venous reflux in the common and superficial femoral, peroneal, and long and short saphenous veins. However, proximal popliteal (above knee) reflux was present in 42 ulcerated legs compared with 31 non-ulcerated legs ($P = 0{\cdot}034$, χ^2 test). Similarly, 39 ulcerated legs had distal (below knee) popliteal vein reflux compared with 26 non-ulcerated legs ($P = 0{\cdot}024$, χ^2 test). There were also significant differences in reflux between ulcerated and non-ulcerated legs in the posterior and anterior tibial veins, although the proportion of uninformative scans at these sites was higher.

Deep and superficial reflux is common in legs unaffected by the typical skin changes of chronic venous insufficiency. However, in the ulcerated leg reflux is more common in the popliteal, anterior and posterior tibial venous segments.

CD11b and CD62L as markers of adhesion in experimental venous hypertension

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Neutrophil degranulation has been reported previously during venous hypertension in normal subjects and in patients with venous disease, but little assessment of adhesion has been made. Expression of the integrin CD11b on neutrophils and monocytes, and the selectin CD62L on neutrophils, monocytes and lymphocytes, has been measured in a group of 25 normal volunteers with no evidence of venous disease. These molecules are expressed on the surface of white blood cells during adhesion to vascular endothelium.

Blood was taken from a foot vein of the volunteers after lying supine for 30 min. They then stood supported for 30 min to raise venous pressure, after which a second sample was taken; a third sample was taken after returning to the supine position for 10 min. Samples were analysed for full blood count and for CD11b and CD62L, measured using labelled monoclonal antibodies in a flow cytometer.

	Neutrophil		Monocyte		Lymphocyte
	CD11b	CD62L	CD11b	CD62L	CD62L
Basal	4·31	4·1	6·08	1·38	0·33
Standing	3·13	3·71	3·85	1·08	0·25
*P**	< 0·001	0·05	< 0·0001	0·04	0·012
Supine	5·67	3·59	5·07	1·25	0·24
*P**	< 0·001	n.s.	< 0·01	n.s.	n.s.

*Wilcoxon test. n.s., Not significant

There was a fall in the white cell:red cell ratio after standing from median 1·33 to 1·31 ($P = 0·035$, Wilcoxon test) followed by a rise on returning to the supine position (median 1·54, $P < 0·001$) as the white cells returned to the systemic circulation. Neutrophil and monocyte CDllb levels fell on standing, then increased on return to the supine position. CD62L levels fell in both neutrophils and monocytes, with no change in lymphocytes on returning to the supine position. These results show a reduction in the number of white cells leaving a normal limb during short-term venous hypertension, associated with a fall in CD11b expression. This is followed by a rise in the number of white cells on return to dependency, with a significant increase in neutrophil CD11b expression. The results suggest increased binding of neutrophils to vascular endothelium during short-term venous hypertension, consistent with the white cell trapping hypothesis of venous ulceration.

Relationship between venous reflux as demonstrated by duplex ultrasonography and healing of chronic venous ulceration

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Venous ulceration is estimated to affect 1 per cent of the adult population, and is generally accepted to occur as a result of venous hypertension. This prospective study aimed to determine the relationship between deep and superficial venous reflux and healing of chronic venous ulceration.

Some 155 patients with chronic venous ulcers underwent duplex ultrasonography before being treated with compression bandaging at a hospital-based venous clinic. At 24 weeks, 104 ulcers (67 per cent) had healed. There was no significant difference in the pattern of either deep or superficial venous reflux between the healed and non-healed groups except with respect to the popliteal vein. In healed legs, 39 scans (38 per cent) indicated competence of the above-knee popliteal vein compared with five scans (10 per cent) in the non-healed group ($P < 0·001$, χ^2 test). Similarly 44 scans (42 per cent) showed below-knee popliteal vein competence in the healed legs compared with only five scans (10 per cent) performed in legs remaining ulcerated ($P < 0·001$, χ^2 test).

Popliteal vein incompetence in patients with venous ulceration is an indicator of poor prognosis and its recognition will allow more effective planning of patient care and use of resources.

Microvessel density in human wound healing: an immunohistochemical study

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Angiogenesis is an essential feature of human wound healing. Determination of microvessel density has been used extensively as an index of tumour angiogenesis but has not previously been applied to wound biology.

With ethical committee approval, 6-mm punch biopsies were taken from the edge of open granulating surgical wounds 1 week after operation and every 2 weeks until healed in five patients. A biopsy taken at operation was included in the analysis. Seven normal skin biopsies were used for comparison. Microvessels were visualized with an antihuman factor VIII antibody. Using a light microscope at × 250 magnification, commencing immediately below the leading epithelial edge, triplicate counts were made vertically downwards to the lower end of the section. Counting was repeated one field behind and one in front of the leading edge. Microvessel density in normal skin and operative biopsies was determined at the area of maximum vascularity, immediately below the epidermis.

Mean microvessel density for normal skin was 12·48 (range 7·67–19·34). No difference was found between the counts below, behind and in front of the leading edge. These data were therefore pooled. Microvessel density was inversely related to the depth below the leading edge, there being a significant decrease in mean(s.d.) microvessel density between depths of 0 mm (27·65(12·69)) and 2·04 mm (18·29(9·12); $P = 0·016$, Students t test) and 0 mm and 4·76 mm (15·15(9·97); $P = 0·05$). The mean(s.d.) maximal microvessel density for all time points was 47·27(5·38), 3·5 times that for normal skin. As the healing time varied between 4 and 10 weeks microvessel density values were normalized to values at operation and then at 25 per cent, 50 per cent and 75 per cent of the total healing time (T) for each patient.

Operation	25 per cent T	50 per cent T	75 per cent T
15·60(2·10)	21·25(5·47)*	36·03(8·50)*	25·58(8·16)*

Values are mean(s.d.) for all patients at each time point. *$P < 0·05$ *versus* operation (Student's t test)

These data illustrate that significant changes in microvessel density occur during the course of wound healing in a temporally and spatially coordinated manner, and may provide a useful basis for the study of non-healing wounds and the effects of potential therapeutic agents.

Control of scar contraction by dermal extracts

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It is a well known clinical observation that when a raw area is covered by a thin split-thickness graft, the grafted area contracts substantially, yet when a full-thickness free skin graft is applied no contraction occurs. This suggests that the dermis plays a key role in the modulation of such contraction; the mechanism is unknown. The authors demonstrated previously that extracts from human dermis can inhibit fibroblast multiplication and migration in culture *in vitro*. The aim of the study, therefore, was to investigate the effect of human dermal extracts on collagen contraction *in vitro*.

Human dermis was obtained from the excess skin removed during operations for breast reduction or abdominoplasty. The dermal extracts were prepared using sequential solvents: water, normal saline, saline $1\ \text{mol}\,\text{l}^{-1}$, citrate buffer and urea. The hydrated collagen gel culture was used as a model for wound contraction. Fifty collagen gel plates were seeded with human fibroblasts; 25 gels were treated with the different extracts (five gel plates for each dermal extract) and 25 gels were untreated (control). The diameter (mm) of each gel was recorded daily for 4 days.

Citrate buffer extract showed the most marked inhibition of collagen gel contraction ($P<0{\cdot}01$, Bonferroni test), particularly on days 1 and 2 (mean(s.d.) diameter 19·3(0·7) and 17·6(0·8) mm respectively). Thus, human dermis contains factor(s) that can inhibit the ability of fibroblasts to cause contraction. The dermal factor(s) can be extracted by citrate buffer (pH 3·6). Investigations are in progress to isolate and characterize the active principle in this extract.

Regulatory and proinflammatory roles of interleukin 6 in intra-abdominal sepsis

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The magnitude of the systemic inflammatory response is a major determinant of outcome from intra-abdominal sepsis. The mediators associated with this response have been well characterized, interleukin (IL) 6 being frequently associated with death. The acute phase response, and levels of IL-6 and the natural cytokine antagonist type I soluble tumour necrosis factor receptor (sTNFr) were measured in 57 patients with sepsis syndrome to determine their influence on outcome. Intra-abdominal sepsis was diagnosed at laparotomy; subjects then underwent blood sampling on entry to the intensive care unit and at intervals for 10 days; C-reactive protein (CRP), IL-6 and sTNFr levels were measured by enzyme-linked immunosorbent assay. The overall mortality rate was 33 of 57 (58 per cent). The results for these parameters and Acute Physiology Score (APS) are shown below:

	APS	CRP	Albumin	IL-6	sTNFr
Non-survivors	19(1)	206(18)	24·1(1·6)	41 234(20 877)	18·6(1·7)
Survivors	14(1)	235(15)	26·2(1·2)	6480(2155)	12·4(1·0)
*P**	0·003	0·25	0·31	0·017	0·005

Values are mean(s.e.m.). **t* Test; non-survivors *versus* survivors

APS of non-survivors was greater at study entry; peak serum sTNFr was also higher in this group. Despite peak IL-6 levels also being greater in non-survivors, CRP and albumin levels (a measure of acute phase response) were similar irrespective of outcome. IL-6 has recently been demonstrated to be anti-inflammatory by inducing the release of the endogenous cytokine antagonist sTNFr. Thus whilst non-survivors displayed a greater physiological upset, outcome was independent of the level of the acute phase response. IL-6 secretion over and above that required to induce a maximal acute phase response may initiate the secretion of sTNFr. Regulatory complexities as observed in this study highlight the difficulties in interpreting the significance of cytokine data and the limitations of current immunotherapy strategies.

Modulation of neutrophil–endothelial adhesion by intravascular interleukin 8

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Interleukin 8 (IL-8) is a cytokine that can both promote and downregulate neutrophil (PMN)–endothelial adhesion at sites of inflammation. The effect of IL-8 and other chemoattractants in the apical compartment on PMN–endothelial adhesion was studied using a parallel-plate flow chamber that simulated the pathophysiological conditions at the endothelial surface. Pre-exposure of PMNs to IL-8 or platelet-activating factor (PAF) before perfusion induced L-selectin shedding resulting in decreased attachment under flow to activated endothelial cells by 69 per cent (539 *versus* 1767 PMNs per mm^2 in control) and 62 per cent (667 *versus* 1767 PMNs per mm^2 in control) respectively ($n=5$; $P<0{\cdot}001$). In spite of activation of CD11b/CD18, transmigration was dramatically inhibited in the presence of IL-8. In separate experiments, unstimulated PMNs were allowed to adhere to activated endothelial cells for 2 min following which chemoattractant was perfused for 15 min. IL-8 ($1\ \text{nmol}\,\text{l}^{-1}$) after 15 min induced detachment of mean(s.d.) 56·3(10·4) per cent of PMNs ($n=4$; $P<0{\cdot}01$) that were stably adherent to activated endothelial cells. Transmigration was inhibited by a mean(s.d.) of 92(5) per cent (97 PMNs per mm^2 (IL-8) *versus* 535 PMNs per mm^2 (control); $P<0{\cdot}01$). C5a and formylated bacterial peptide, but not PAF, exhibited the same concentration-dependent effects as IL-8 on PMN adhesion and transmigration. This suggests that IL-8-induced detachment was not due to collapse of endogenous chemotaxin gradients. To further examine detachment induced by IL-8, PMNs were adhered to fibrinogen (FG)-coated glass (CD11b/CD18 dependent). PMNs that adhered to FG-coated glass were not susceptible to detachment by IL-8 or PAF indicating differences in the nature of the bonds formed by PMNs with endothelial cells and other surfaces. These data provide insight into the mechanisms by which intravascular IL-8 and other chemoattractants may modulate neutrophil adhesive interactions with vascular endothelium.

Chronic human wounds are associated with raised tissue levels of matrix metalloproteinase 9 (92-kDa gelatinase)

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Human dermal repair is characterized by a dynamic series of events that require coordinated sequential synthesis and degradation of various extracellular matrix components. Expression of members of the matrix metalloproteinase (MMP) family of enzymes during wound healing is well recognized and increased activity of the gelatinases, especially MMP-9, has been found in fluid from chronic ulcers. The aim of this study was to examine the tissue levels and spatial expression of MMP-9 in acute and chronic human wounds.

A total of 39 punch biopsies was excised from the edge and base of eight acute granulating surgical wounds at 2-weekly intervals over the course of healing, with ethical committee approval. Representative transverse sections through complete chronic leg ulcers were also obtained from seven patients immediately following limb amputation for infection or critical ischaemia. Immunocytochemistry was performed using a previously characterized polyclonal antibody to MMP-9. Contiguous sections were used for gelatin zymography to demonstrate tissue levels of MMP-9, and bands of gelatin digestion were quantified using a scanning laser densitometer and volume–intensity analysis.

Tissue MMP-9 levels were raised in both acute wounds $P<0\cdot0001$, Mann–Whitney *U* test) and chronic ulcers ($P<0\cdot001$) compared with normal skin. Chronic wounds displayed generally higher levels of enzyme than acute wounds ($P<0\cdot005$). Immunoreactivity of epithelial cells at the migrating tip was detected in early acute but not chronic wounds. Matrix staining adjacent to the epithelial tip was seen in both acute and chronic wounds but was generally more intense in chronic ulcers, correlating well with the levels of activity seen on zymography.

These data show that increased tissue levels of MMP-9 occur in both healing wounds and chronic ulcers but that significantly higher levels are associated with the chronic state. Epithelial expression was seen only in acute wounds although matrix staining adjacent to the epithelial tip was strongest in chronic ulcers. This different pattern of enzyme expression may represent either a cause of, or a response to, the chronic nature of the non-healing wound.

Inhibition of natural cytotoxicity with eicosapentaenoic and docosahexaenoic acids: possible mechanism(s)

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It has been postulated that patients with inflammatory bowel disease (IBD) have altered status of natural cytotoxicity, in particular natural killer (NK) and lymphokine-activated killer (LAK) cell activities. A viral infectious agent within the gastrointestinal tract is believed to trigger an abnormal autoimmune response, inducing NK cell cytotoxic activity against virus-infected gut epithelial cells. The authors have previously shown that in patients with IBD the omega-3 essential fatty acids (EFAs), eicosapentaenoic acid and docosahexaenoic acid, specifically inhibit natural cytotoxicity with improvement in disease activity. Also, reduced serum interleukin 2 (IL-2) levels with EFA supplementation have been documented. The aim of this study, therefore, was to evaluate the possible mechanism(s) involved in this inhibition, in particular alteration of production of IL-2 and the EFA metabolite leukotriene B4 (LTB4), both known to modulate NK cell activity.

Over a period of 6 months blood mononuclear (BMN) cells from 18 patients with active proctocolitis (EFA supplementation $n=9$, placebo $n=9$) were isolated by gradient centrifugation and cryopreserved. The EFA group had significantly reduced BMN cell NK activity (chromium-51 release, K562 cell line) compared with the placebo group (32·4 and 2·7 lytic units (number of effector cells required to kill 30 per cent of target cells) respectively; $P<0\cdot05$, Mann–Whitney *U* test). In the EFA group, incubation of these BMN cells (2×10^6 ml^{-1}) for 72 h with IL-2 250 units ml^{-1} reversed the NK inhibition. In patients with IBD, serum levels of LTB4 positively correlated with NK cytotoxicity ($r=0\cdot906$, $P<0\cdot05$). After 6 months of omega-3 EFA supplementation, serum levels of LTB4 were undetectable, with concurrent significant reduction in NK cell cytotoxic activity.

These findings suggest a possible mechanism for EFA-induced inhibition of natural cytotoxicity.

Decreased interleukin 2 and increased tumour necrosis factor production by human mononuclear cells may facilitate an exaggerated response to circulating endotoxins

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Endotoxaemia in humans is associated with an acute-phase response, but levels of endotoxins do not relate to the severity of this response. Tumour necrosis factor (TNF) is thought to mediate the effects of endotoxins. Sensitivity to endotoxin and TNF is increased in the cancer state. This may account for the lack of correlation between clinical outcome and levels of TNF and endotoxin. The authors examined whether an index (TNF/interleukin 2 (IL-2)), incorporating tests of lymphocyte function and spontaneous mononuclear activity (peripheral blood mononuclear cell (PBMC) IL-2 production and basal PBMC TNF production respectively), might reflect the extent of the inflammatory response to endogenous endotoxin.

Blood was drawn from a pool of five healthy volunteers and eight patients with metastatic cancer. *In vitro* spontaneous PBMC TNF production (WEHI bioassay), PBMC IL-2 production (CTLL-2 bioassay) in response to phytohaemagglutinin (PHA), serum C-reactive protein (CRP) and albumin, percentage weight change over the previous 6 months, lean body mass index (BMI) and BMI (calculated from indices of height and weight), and survival of patients with cancer were documented.

Significant levels of endotoxin were found in four of five volunteers (median 4 (range 1–6·5) pg ml^{-1}) and five of seven patients with cancer (18 (2–27·5) pg ml^{-1}). Median (range) spontaneous TNF production in these subjects was 44 (39–208) pg ml^{-1} (volunteers) and 121 (16–267) pg ml^{-1} (patients). Neither the level of endotoxin nor the amount of PBMC TNF production correlated with CRP, albumin, weight change, BMI, lean BMI or white cell count (WCC). The index, TNF/IL-2, multiplied by the levels of circulating endotoxin in the nine subjects with evidence of endotoxaemia correlated with CRP ($r_s=0\cdot72$, $P=0\cdot03$), albumin ($r_s=0\cdot88$, $P=0\cdot002$), CRP/albumin ($r_s=0\cdot78$, $P=0\cdot013$), WCC ($r_s=0\cdot67$, $P=0\cdot05$), weight change ($r_s=0\cdot88$, $P=0\cdot01$), BMI ($r_s=0\cdot88$, $P=0\cdot001$) and lean BMI ($r_s=0\cdot77$, $P=0\cdot016$), despite considerable overlap in all of these parameters between the patients and volunteers.

The clinical impact of endotoxaemia may be influenced by the degree of impairment of lymphocyte IL-2 production, the spontaneous production of TNF and the levels of circulating endotoxin.

Calcium responsiveness of human parathyroid cells from patients with secondary hyperparathyroidism

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Secondary hyperparathyroidism presents as hyperplastic or adenomatous change in response to disturbed metabolic regulatory factors, such as chronic renal failure. A shift in calcium set point, possibly induced by abnormal signalling from the calcium receptor, may play a role in its pathogenesis.

Quantitative microfluorimetry was used in single parathyroid cells derived from glands of patients with secondary hyperparathyroidism ($n=11$) to investigate intracellular calcium ($[Ca]_i$) responses to varying extracellular calcium levels ($[Ca]_e$), lanthanum (La^{3+}) and thapsigargin (THAP; an inhibitor of Ca^{2+}-ATPase of the IP_3-sensitive Ca^{2+} stores). Ratios of fluorescence signals allowed derivation of $[Ca]_i$ in nanomoles and statistical analysis of differences was done using Student's *t* test.

Cells in which an increase in $[Ca]_i$ appeared in response to changes in $[Ca]_e$ from 0·5–3 mmol l^{-1} were classified as calcium responsive and others as calcium non responsive. The peak $[Ca]_i$ after increasing $[Ca]_e$ to 3 mmol l^{-1} was dependent on the amplitude of the step: moving from 1·8 mmol l^{-1} and 0·5 mmol l^{-1} $[Ca]_e$ induced a mean(s.d.) increase to 477·4(26·1) nmol l^{-1} *versus* 533·5(23·4) nmol l^{-1} respectively ($n = 54$ cells, $P = 0·06$). When perfused with 5mmol l^{-1} $[Ca]_e$, calcium-sensitive cells responded with a sharp and sustained $[Ca]_i$ increase, while non-responsive cells produced only a transient spike. An important variability of basal and peak $[Ca]_i$ was observed in calcium-responsive cells.

La^{3+} (1mmol l^{-1}, in calcium-free solution) evoked peaks of $[Ca]_i$ in both calcium-responsive (to mean(s.d.) 398 (17·5) nmol l^{-1}, $n = 52$ cells) and non-responsive cells (to 318 (14·2) nmol l^{-1}, $n = 18$ cells), proving that calcium mobilization was functional in both types of cell.

Incubation with THAP 3 mmol l^{-1} for 10 min induced a significant rise in $[Ca]_i$ from mean(s.d.) 286·2 (14·2) nmol l^{-1} to 438·7(21·3) nmol l^{-1} ($n = 80$ cells) at 0·5mmol l^{-1} $[Ca]_e$, but induced only a minimal change in calcium-free medium. When stepping from zero or 0·5mmol l^{-1} to 1·8 mmol l^{-1} $[Ca]_e$ after THAP incubation, mean(s.d.) $[Ca]_i$ increased to 559·7(25·9) nmol l^{-1} (compared with 334·2 (27·4) nmol l^{-1} at 1·8 mmol l^{-1} $[Ca]_e$ before THAP; $n = 47$ cells, $P < 0·01$), and no further increase was induced by stepping to 3 mmol l^{-1} $[Ca]_e$. This effect appeared to be due to increased calcium entry, rather than mobilization, since THAP abolished responses to La^{3+} and therefore emptied internal stores. THAP caused similar changes in $[Ca]_i$ in calcium-non-responsive cells.

These data suggest that calcium mobilization and entry mechanisms are functional in parathyroid cells from patients with secondary hyperparathyroidism and cell subpopulations exist with a lower calcium sensitivity at a stage proximal to these processes. This might explain the variability of gland response to altered metabolic factors in secondary hyperparathyroidism.

Evaluation of skills in minimal access surgery using endoscopic psychomotor tester

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A microprocessor-controlled psychomotor tester has been developed to assess psychomotor abilities relevant to minimal access surgery. It consists of a probe that can be inserted through holes in an irregular target object. The system records the spatial coordinates of the tip of the probe, the force exerted on the target and the execution time of the task. An error is registered on contact of the probe with the rim of the hole for 1 s or more and the subject has to reattempt the same target. A two-dimensional display system employing a forward viewing Hopkins II telescope was used. Each test run consisted of ten target holes selected in a random sequence. Two groups of right-handed and left-handed medical students, each of ten individuals, were involved. After a prestudy session, each individual performed two test runs with one hand followed by two runs with the other hand. These test runs were repeated 1 week later by all subjects.

Practice improved the execution time with a mean of 52 s in the first run and 36 s in the fourth ($P < 0·001$, repeated measures analysis of variance). A significant difference in the error rate and first-time accuracy was observed between subjects ($P < 0·001$ and $P < 0·001$ respectively) and between the dominant and non-dominant hand ($P < 0·001$ and $P < 0·03$ respectively) with no significant change with practice (generalized linear interactive model for a Poisson fit). Right-handed subjects performed better with either hand in terms of error rate ($P < 0·001$) and first-time accuracy ($P < 0·001$) than left-handed individuals.

Objective evaluation of performance in an endoscopic environment is a practical proposition. Certain parameters that improve with practice reflect the effect of practice while others, which do not, reflect innate abilities.

Increased CD11b receptor expression after injury is an independent marker of early neutrophil priming

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Neutrophil (PMN)-mediated tissue injury is an important mechanism of multiple organ failure after injury. *In vitro* studies have shown that increased CD11b adhesion receptor expression and PMN priming for enhanced superoxide (O_2^-) release are necessary steps for PMN-mediated cytotoxicity. It was therefore hypothesized that circulating PMNs in high-risk trauma patients would have early synchronous increases in CD11b and O_2^- radical expression.

Central venous blood was sampled from 17 high-risk trauma patients (Injury Severity Score more than 15 and more than 6 units blood transfused) at 6 and 12 h after injury. Ten healthy donors served as controls. PMNs were stained with fluorescent monoclonal antibodies against CD11b receptors and assessed by flow cytometry. PMN O_2^- release was measured by kinetic cytochrome C reduction and priming defined as enhanced O_2^- release after stimulation with 1 μmol l^{-1} *N*-formyl-methyl-leucyl-phenylalanine.

Mean(s.e.m.) CD11b expression was increased at 6 (3·52(0·33) mean fluorescence intensity) and 12 (3·62(0·29) mean fluorescence intensity) h after trauma (control 2·65(0·14) mean fluorescence intensity; $P < 0·01$, unpaired *t* test). Similarly, PMNs were primed for enhanced O_2^- release at 6 (mean(s.e.m.) 1·74(0·31) nmol O_2^- per min per $1·3 \times 10^6$ PMNs) and 12 (1·76(0·37) nmol min^{-1}) h after trauma (control 0·60(0·06) nmol min^{-1}, $P < 0·01$). However, when results were analysed for individual patients, there was no correlation between CD11b expression and priming for O_2^- release ($r = 0·09$, $P > 0·05$). Increased expression of CD11b receptors and O_2^- radicals by circulating PMNs after trauma are thus not synchronous events. This suggests disparate underlying molecular mechanisms, and that increased CD11b expression is an independent marker of PMN priming.

Age-related changes in proinflammatory cytokine production by peripheral blood T lymphocytes

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The immune response to sepsis and trauma is altered with increasing age. It was hypothesized that changes in proinflammatory cytokine production may play a role in this phenomenon. To investigate this hypothesis a novel technique of proinflammatory cytokine detection in peripheral blood mononuclear cells (PBMCs) using flow cytometry was developed. PBMCs were obtained from healthy donors who were divided into three groups according to age: 20–39 years (group 1, $n = 8$), 40–54 years (group 2, $n = 8$) and more than 55 years old (group 3, $n = 7$). PBMCs were activated for 24, 48 or 72 h with phorbol myristate acetate. Cells were stained with monoclonal antibodies to the relevant cytokine (tumour necrosis factor (TNF) α, interleukin (IL) 1β, IL-6) at each time point and fluorescence was measured using flow cytometry.

	Time			
	0 h	24 h	48 h	72 h
TNF stimulated				
Group 1	17·4(1·4)	36·4(3·0)	35·1(4·1)	31·4(3·2)*
Group 2	14·8(1·3)	31·8(6·4)	41·4(6·8)	40·9(5·3)*
Group 3	13·4(0·8)	30·9(4·0)	46·9(7·1)	51·9(5·5)*
IL-6 stimulated				
Group 1	19·7(1·7)	31·6(1·78)	36·3(6·2)	33·5(3·4)
Group 2	20·25(1·8)	36·3(5·9)	47·6(8·4)	46·5(11·5)
Group 3	18·6(1·5)	35·4(3·8)	61·6(13·0)	59·6(12·0)

Values are mean(s.d.). *$P < 0·025$ group difference (ANOVA)

No IL-1β was detected in any of the T cell samples. Overall increases in both TNF-α and IL-6 detection were seen with increasing age after stimulation. The difference in TNF-α and IL-6 detection between the different age groups may help explain the exaggerated inflammatory responses seen in elderly patients. Further clinical studies examining T cells and other cell subpopulations should increase our understanding of this phenomenon.

Neutrophil-derived hypochlorous acid production in multiple organ failure-related fungaemia

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Neutrophil-derived hypochlorous acid (PMN-HOCl) is a potent bactericidal and fungicidal agent. PMNs from patients with multiple organ failure (MOF) are known to have depressed ability to inhibit *Candida albicans*. Antifungal agents are effective in decreasing mortality rate in patients with MOF and fungaemia, a function thought to result from improved PMN-HOCl production. The rate of production of PMN-HOCl was determined in a small series of patients with *C. albicans* fungaemia before and after institution of antifungal therapy.

Eleven patients with MOF were recruited. Four (three women, 1 man; age range 58–72 years) had culture-positive *C. albicans* fungaemia (group 1); seven (four men, three women; age range 54–75 years) acted as controls (group 2). Baseline HOCl assays were performed on blood obtained from group 1 patients after the fungaemia was detected and before starting antifungal therapy. PMNs were obtained from blood by discontinuous two-step centrifugation on Ficoll–hypaque density gradients. PMN-HOCl production was then determined by the taurine chlorination method using ultraviolet spectrophotometry. All assays were performed in triplicate.

The maximum PMN-HOCl production rate for group 1 was 0·242 (median 0·206) nmol per 10^6 PMNs per min before treatment and 0·791 (median 0·582) nmol per 10^6 PMNs per min after treatment ($P<0·01$, Mann–Whitney *U* test). The PMN-HOCl production rate for group 1 after treatment was similar to that for group 2 (*t* test).

These findings suggest that antifungal treatment improves PMN-HOCl production in patients with MOF and *C. albicans* fungaemia, and may help explain the decrease in mortality rate in this group of patients.

Serum soluble tumour necrosis factor receptor concentrations are associated with disease severity in acute pancreatitis

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Excessive production of tumour necrosis factor (TNF) is believed to be responsible for many of the features of septic shock, but its role in acute pancreatitis remains controversial as TNF is often undetectable in the serum of patients, even those with severe disease. Cells expressing surface TNF receptors downregulate their responsiveness following exposure to TNF by receptor shedding. Release of these soluble TNF receptors (sTNFR$_{55}$ and sTNFR$_{75}$ fragments) appears to reflect the degree of TNF-induced inflammation. This study assessed the serum concentration of TNF and sTNFR in 58 patients with acute pancreatitis on the first day of admission. The clinical course of the patients was followed prospectively, allowing retrospective categorization of patients into those with mild ($n=30$) or severe ($n=28$) disease (Atlanta classification). Of patients with severe disease, 18 developed local pancreatic complications alone and ten developed organ failure (Goris score). TNF was detected in only 18 patients, one with mild disease, ten who developed local complications only and seven who developed organ failure (minimum detection level 15 pg ml^{-1}). sTNFR was detectable in all patients. The results are given in the *Table*.

Severity	TNF (pg ml^{-1})	sTNFR$_{55}$ (pg ml^{-1})	sTNFR$_{75}$ (pg ml^{-1})
Mild	15 (15–15)	1058 (652–1388)	1312 (963–1927)
Local complication	17·8 (15–23·8)	2125 (1751–2717)	2687 (1760–3239)
Organ failure	22·6 (15–75·1)	4625 (3615–5307)	4916 (2704–11363)
*P**	0·34	0·001	0·001

Values are median (interquartile range). *Kruskal–Wallis test

Patients with acute pancreatitis who subsequently developed organ failure were associated with significantly increased levels on admission of both sTNFR$_{55}$ and sTNFR$_{75}$ but not TNF. If sTNFR release correlates with TNF-induced inflammation, these findings would support the role of TNF in mediating inflammatory events early in the course of the disease.

Presenting symptom influences outcome following carotid endarterectomy

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Outcome-based standards have been set for carotid endarterectomy. However, outcome is dependent on many factors, including patient-related variables.

Some 460 consecutive patients undergoing carotid endarterectomy for symptomatic 60–99 per cent internal carotid stenosis have been followed up clinically and by duplex surveillance prospectively at 3, 6, 9 and 12 months and then annually for a mean of 40 months.

Multiple logistic regression analysis was performed taking death and stroke as dependent variables and entering 20 independent variables into the model. A history of crescendo transient ischaemic attack (TIA) ($P=0·003$; $P=0·0002$) and female sex ($P=0·02$; $P=0·0001$) was associated with both death and stroke within 30 days of operation respectively. Death between 1 and 36 months was associated with ischaemic heart disease ($P=0·03$) and diabetes ($P=0·04$), whereas stroke was associated with small internal carotid external diameter ($P=0·02$).

Life-table analysis confirmed an association between presenting symptom and outcome:

Presenting symptom	Survival at 36 months (%)	Stroke rate at 36 months (%)
Amaurosis fugax	98	0
TIA	84	5
Transient stroke	66	13
Established stroke	85	8
Progressive stroke	77	27
Crescendo TIA	67	26

Thus survival and avoidance of stroke in patients presenting with amaurosis fugax was significantly better than that for those with all other presentations ($P<0·01$). Similarly, patients presenting with crescendo TIA had a significantly worse prognosis than other patients ($P<0·05$).

Presenting symptom significantly determines outcome following carotid endarterectomy. This should be considered both in patient selection and comparison of patient series.

Supplementation of intravenous nutrition with glutamine after major surgery: does it improve immune function?

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Glutamine is an important fuel for lymphocytes and macrophages and it has been suggested that glutamine provision may help to maintain immune function, particularly when the body is stressed after surgery.

A prospective randomized study was performed on 24 patients undergoing major resection for gastro-oesophageal malignancy. Intravenous nutrition (IVN) was commenced on the day of surgery and continued for a mean of 8 days after operation. Patients were randomized to receive either glutamine-supplemented IVN (group A) or a standard preparation with equivalent protein content (0·2 g kg^{-1}) (group B). Natural killer (NK) cell cytolytic activity (chromium release assay) and T cell proliferation in response to phytohaemagglutinin and staphylococcal enterotoxin (thymidine uptake assay) were measured before operation and on days 7 and 14 after operation.

	Day 0	Day 7	Day 14
NK cell cytotoxicity*			
Group A	29	18	22
Group B	41	32	30
T cell proliferation†			
Group A	64	11	20
Group B	47	17	37

*Expressed as percentage lysis at lymphocyte : target ratio of 30 : 1; †stimulation index, calculated as c.p.m. for lymphocytes plus antigen/c.p.m. for lymphocytes alone

There was no significant difference in immune function between the two groups before operation or on days 2 and 7. Supplementation of IVN with glutamine following major surgery did not significantly affect the degree of immunosuppression in this group of patients.

Interleukin 10 inhibits endotoxin-induced monocyte major histocompatibility complex class II upregulation after surgery

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Interleukin 10 (IL-10) is a T cell and monocyte-derived cytokine that can downregulate monocyte functions such as the lipopolysaccharide (LPS)-induced increase in monocyte major histocompatibility complex (MHC) class II antigen expression. LPS-induced monocyte MHC class II expression is impaired and IL-10 gene expression upregulated following major resectional surgery and trauma. This study aimed to characterize further the relationship between IL-10 induction and surgically induced impairment of monocyte function by inhibiting the activity of IL-10 in LPS-activated peripheral blood mononuclear cells (PBMC) after surgery in order to determine the effects of this inhibition on LPS-induced MHC class II expression after major surgical injury.

PBMC were obtained from 18 patients before and 24 h after major abdominal resectional surgery and cultured with and without 100 ng ml^{-1} LPS for 24 h in the absence or presence of 2 μg ml^{-1} neutralizing anti-IL-10 antibody. PBMC were harvested and the level of monocyte MHC class II expression quantified by dual colour flow cytometry.

Results, expressed as the percentage(s.e.m.) upregulation of MHC class II induced by LPS over baseline, are given here.

Day	LPS alone	LPS + IL-10 blocking antibody
0	251(24·4)	255(25·5)
1	160(10·1)*	215(11·6)†

*$P<0{\cdot}05$ *versus* day 0; †$P<0{\cdot}05$ *versus* LPS alone (....test)

Thus, anti-IL-10 blocking antibody had no impact on the level of LPS-induced monocyte MHC class II expression before operation but augmented the surgically suppressed level of expression. These results confirm that monocyte MHC class II expression induced by LPS is diminished by major surgery but that this can be prevented by a neutralizing anti-IL-10 antibody.

It is concluded that endogenous IL-10 plays a role in immunosuppression after surgery and this may have therapeutic implications.

Hyperaemia after carotid endarterectomy: pathological or physiological

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Previous studies (transcranial Doppler ultrasonography (TCD), xenon washout) suggest that carotid endarterectomy (CE) is usually followed by transient hyperaemia which may cause headaches or fits (15 per cent of patients) and stroke (1 per cent: cerebral oedema or haemorrhage). It is believed that hyperaemia reflects reperfusion in patients with impaired cerebrovascular reserve and cerebral vasodilatation and that failure of autoregulation allows blood flow in excess of requirements. Thus, hyperaemia represents 'luxury' perfusion which should be accompanied by an apparent reduction in cerebral oxygen extraction.

This concept was examined in 38 patients who had CE (20 general anaesthesia (GA), and 18 regional anaesthesia (RA)) by assessing middle cerebral artery velocity (MCAV) with TCD, global oxygen extraction (continuous jugular venous oximetry: jugular venous saturation (JvS_{O_2})) and tissue oxygen (O_2) supply/demand (near infrared spectroscopy: oxyhaemoglobin ($Hb0_2$), and cytochrome oxidase (caa3)). Some 10 min after reperfusion mean MCAV increased in 16 of 20 patients who had GA (median 35 (interquartile range (IQR)) 27–68) per cent) and 12 of 18 patients who had RA (median 37 (IQR 24–61) per cent) and persisted for more than 24 h. In patients who had RA hyperaemia was not associated with alterations in JvS_{O_2}, $Hb0_2$ or caa3, suggesting that this response is either physiological or that MCAV changes are the result of vasospasm. In contrast JvS_{O_2} increased (reduced global 0_2 extraction) in patients who had GA (median 6 (IQR 0–15) per cent) and this correlated with MCAV changes ($r=0{\cdot}65$, $P<0{\cdot}01$). Thus, while local blood flow (0_2 supply) and demand were matched (unchanged $Hb0_2$, caa3), global luxury perfusion (increased JvS_{O_2}) occurred, consistent with arteriovenous shunting.

It would thus appear that the mechanisms responsible for increased MCAV following CE are complex and that the apparent hyperaemia does not represent tissue hyperperfusion or reflect impaired cerebrovascular reserve.

Enteral nutrition with supplemental arginine in patients after oesophageal resection

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Perioperative nutritional intervention has been proposed to improve host defence mechanisms and reduce postoperative morbidity. Individual nutrient substrates have been shown to improve immunological cellular functions in laboratory and clinical studies. Some 67 patients undergoing oesophageal resection were entered into three sequential prospective randomized clinical trials which addressed the effect of arginine supplementation on clinical outome. This analysis allows evaluation of a consecutive homogeneous series of patients treated for one type of malignant disease.

	Arginine supplement	Controls
No. of patients	33	34
Caloric intake day^{-1}	1296(312)	1164(477)
Nitrogen intake day^{-1}	12·2(3·6)	10·4(4·6)
Infectious/wound complications	2 (6%)	9 (26%)*
Other complications	10 (30%)	8 (24%)

Values are mean(s.e.m.). *$P<0\cdot05$ *versus* patients given arginine-supplemented diet

In the supplemented diet group, two patients experienced complications that were classified as infectious; neither of these had a wound healing complication. In the standard diet group, eight experienced infections and another had only wound healing complications. The incidence of infectious and wound complications was significantly different between the supplemented (6 per cent) and standard (26 per cent) groups. Arginine supplementation of postoperative enteral feeding significantly reduced infectious and wound complications after oesophageal resection. Further clinical trials are required to assess more thoroughly the clinical benefits of specific nutrients in the treatment of patients with oesophageal cancer.

Tissue factor expression modulates invasion of pancreatic cancer cells

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Tissue factor (TF), the transmembrane cellular receptor that is the physiological initiator of blood coagulation, is not expressed in normal pancreatic tissue, but in adenocarcinoma of the pancreas its expression increases with progressive dedifferentiation. The effect of TF gene expression on *in vitro* invasion by the human pancreatic carcinoma cell line Mia Paca was investigated.

The full length TF gene (1360 base pairs) was cloned into the plasmid DNA vector pcDNA3 in sense and antisense orientations. Diagnostic DNA digests confirmed correct orientation of the cloned genes. These vectors were used to transfect the Mia Paca cell line *in vitro* using the lipofectin method. Expression of TF sense gene resulted in a fivefold increase in cell surface procoagulant activity from 7·8 thromboplastin units per 10^4 cells for wild type to 40·0 units ($P=0\cdot0001$). There was a small reduction in procoagulant activity for the TF/antisense clones to 7·6 units per 10^4 cells. The total antigenic content of TF gene product (sense or antisense) markedly increased from 160 pg mg^{-1} for wild type to 7733 pg mg^{-1} for sense and 856 pg mg^{-1} for antisense. *In vitro* invasion was assessed in a standard matrigel assay by counting the number of cells per high-power field after haematoxylin and eosin staining. The mean(s.d.) number of cells successfully invading through matrigel was 60·75(13·04) for the wild type and 210·2(57·62) for the TF/sense clone ($P=0\cdot02$; 95 per cent confidence interval (CI) $-276\cdot45$ to $-55\cdot02$) and 42·2(6·43) for the TF/antisense clone ($P=0\cdot09$; 95 per cent CI $-8\cdot11$ to 51·98).

This study is the first to demonstrate that cellular expression of TF may influence the invasion of pancreatic tumour cells.

Feeding the gut in acute pancreatitis: a randomized clinical trial of enteral *versus* parenteral nutrition

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In the critically ill, translocation of bacteria and endotoxin from the gut is increasingly implicated as a potential initiator of the systemic inflammatory response syndrome (SIRS) and sepsis. Furthermore, in patients with major trauma, burns or critical illness, total enteral nutrition (TEN) significantly decreases the acute phase response and incidence of septic complications compared with that in patients given total parenteral nutrition (TPN). Poor outcome in acute pancreatitis is associated with a high incidence of SIRS and sepsis. Thus, TEN may have a therapeutic rationale in acute pancreatitis and the aim of this study was to examine this hypothesis.

Twenty-three patients with acute pancreatitis were evaluated for Glasgow, Acute Physiology and Chronic Health Evaluation (APACHE II) and computed tomography (CT) scan scores, C-reactive protein (CRP), and incidence of SIRS and sepsis on admission. Patients were randomized to receive TPN or TEN for 7 days and then re-evaluated.

There were no significant differences between the two groups on admission. The table shows results expressed as percentage change over 7 days.

	Glasgow	APACHE II	CT scan	CRP
TEN	−50	−33*	0	−49*
TPN	0	−10	0	+10

*$P<0\cdot05$, Wilcoxon signed rank test

Hospital stay was significantly increased in patients given TPN compared with those who received TEN (median 25 (range 15–38) *versus* 15 (range 12–29), $P<0\cdot05$, Mann–Whitney U test). Four patients given TPN required a median of 9·5 (range 5–12) days in the intensive therapy unit (ITU), one with a pancreatic abscess: none given TEN required an ITU stay. In addition, contingency table analysis revealed that the incidence of SIRS significantly decreased in patients given TEN, but not in patients given TPN ($P<0\cdot01$, χ^2 test).

These data suggest that TEN improves disease severity, reduces acute phase response and the incidence of SIRS, despite unchanged pancreatic injury on CT scan. Thus, mucosal feeding, perhaps via improved gut mucosal integrity, modulates the inflammatory and sepsis response in acute pancreatitis towards clinical benefit.

Cardiorespiratory function after elective aortic surgery: the effect of perioperative recombinant human growth hormone

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Cardiorespiratory complications are the predominant source of morbidity in patients undergoing major surgery. Recombinant human growth hormone (rhGH) has previously been shown to be effective in improving respiratory and cardiac function in compromised patients. The aim of this study was to assess the effect of perioperative rhGH on respiratory function in surgical patients. Thirty-three patients gave informed consent for elective infrarenal abdominal aortic aneurysm repair and were randomized to one of three groups: placebo for 6 days before and after surgery (control, $n=12$); Genotropin (GH) 0·31 units kg^{-1} day^{-1} for 6 days before and after surgery (pre and postop

GH, $n = 10$); and placebo for 6 days before and rhGH 0·31 units kg^{-1} day^{-1} for 6 days after surgery (postop GH, $n = 11$). Patients were assessed on days 7 (−7) and 1 (−1) before and 7, 14 and 50 after operation. Respiratory function was assessed using forced expiratory volume in 1 s (FEV1) and arterial partial pressure of oxygen (Pa_{O_2}). Intraoperative cardiac index (CI) was measured after induction of anaesthesia, before and after aortic cross-clamping, after aortic unclamping and at the end of surgery using thermodilution. Results are expressed as change from baseline (day −7 for respiratory data; after induction for cardiac function).

	Preclamp	Postclamp	Postunclamp	End of surgery
Cardiac index (1 per min per m² per BSA)				
Control and postop GH	0·713(0·278)	0·016(0·322)	0·655(0·258)	0·232(0·363)
Preop and postop GH	1·234(0·458)	0·281(0·203)	0·962(0·399)	0·702(0·226)

Values are mean(s.e.m.). BSA, body surface area

	Time after surgery (days)			
	−1	7	14	50*
FEV1 (litres)‡				
Control (placebo)	−0·12(0·08)	−0·52(0·09)	−0·35(0·16)	−0·06(0·09)
Pre and postop GH	0·024(0·04)	−0·31(0·17)	−0·11(0·19)	−0·001(0·09)
Postop GH	0·097(0·07)	−0·34(0·12)	−0·11(0·12)	0·07(0·04)
PaO_2 (kPa)§				
Control (placebo)	−0·319(0·32)	−3·48(0·58)	−1·28(1·65)	−0·83(1·17)
Pre and postop GH	−1·071(0·46)	−1·17(0·64)	0·45(1·14)	−0·85(0·63)
Postop GH	1·157(0·63)	−1·18(0·61)	1·212(2·38)	0·28(0·68)

Values are mean(s.e.m.). *Days 50–60 for P_{aO_2}. †$P < 0·067$. ‡$P < 0·059$; §$P < 0·025$ for group differences with time (two-way analysis of variance)

These results demonstrate that perioperative administration of rhGH improves intraoperative cardiac indices by 50 per cent. Postoperative respiratory function and arterial oxygenation are also improved by 30 per cent with rhGH.

This study suggests that rhGH improves cardiac performance during aortic surgery and prevents postoperative deterioration in pulmonary function.

Effect of acute alterations in afterload on left ventricular subendocardial behaviour in combined coronary artery and aortoiliac disease

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Coronary artery disease (CAD) is common in patients with peripheral vascular disease. To assess acute alterations in left ventricular (LV) afterload on the potentially ischaemic subendocardium, 20 patients (mean(s.d.) age 61 (8) years: 11 men) with combined CAD and aortoiliac disease were studied at arterial reconstructive surgery. Two dimensional guided M modes of LV long axis, representing the subendocardium, were recorded at the left and septal sites of the mitral ring, along with an electrocardiogram and phonocardiogram. Patients were studied before, during aortic clamping and 15 min and 5 days after declamping. Preoperative results were compared with those from 21 normal individuals of similar age. Before clamping long axis systolic and diastolic functions were impaired. During clamping all measurements deteriorated followed by marked improvement (analysis of variance (ANOVA)) after unclamping.

Variables	Normal controls	Patients with CAD				
		Preop	Clamp	15 min	5 days	P*
Total X (cm)	1·5(0·3)	1·0(0·3)	0·9(0·2)	1·1(0·3)	1·2(0·3)	0·001
q-OS (ms)	80(10)	120(25)	135(20)	105(15)	105(20)	0·001
S vel (cm s^{-1})	7·5(1·2)	3·8(1·7)	3·1(1·0)	4·5(1·4)	5·7(2·8)	0·001
L vel (cm s^{-1})	8·5(2·0)	4·0(1·6)	2·9(1·3)	5·0(1·5)	5·4(1·5)	0·001

Values are mean(s.d.). *ANOVA. X, excursion; OS, onset of shortening; S, shortening; L, lengthening; vel, velocity

Thus, in patients with combined CAD and aortoiliac disease, resting LV subendocardial function is abnormal. It deteriorates with an acute increase in afterload and promptly improves with successful peripheral arterial reconstruction. Even in apparently stable CAD, resting subendocardial function is labile, showing marked alterations with changing afterload.

Potential role of thallium-201 scintigraphy in patients undergoing major non-vascular abdominal surgery

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The prognostic value of thallium-201 myocardial scintigraphy in the occurrence of postoperative cardiac events in patients undergoing cardiovascular surgery is well recognized. A prospective study was performed to assess its value in 55 patients over 60 years undergoing major non-vascular abdominal surgery. In each case thallium-201 single photon emission tomography was compared to known clinical risk variables, but the results of the former were not utilized to change routine management. Thirty-day postoperative morbidity and mortality were recorded.

	Cardiac events ($n = 17$)	No cardiac events ($n = 38$)	P
Age (mean(s.d.))	74(7·7)	71·5(6·7)	NS
Prior cardiac history	10	13	NS
Smoking	6	8	NS
Duration of operation (mean(s.d.)) (min)	135(51)	106(38·9)	0·05
Normal thallium-201 scan	4 (1 death)	31	
Abnormal thallium-201 scan	13 (3 deaths)	7	< 0·002

NS, not significant

Cardiac events were cardiac death (four), angina (six), non-fatal myocardial infarction (one), acute left ventricular failure (two) and arrhythmias requiring treatment (four).

In conclusion, preoperative thallium scintigraphy can identify patients undergoing major abdominal surgery who are at risk of a postoperative cardiac event.

Peripheral thrombolysis with tissue-type plasminogen activator causes reperfusion injury

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Peripheral thrombolysis is an established method for the initial treatment of acute leg ischaemia. Accelerated methods of thrombolysis have allowed patients with severe ischaemia to be treated without recourse to surgery. Information from a national database on thrombolysis has shown a possible increase in reperfusion injury. The aim of this study was to identify evidence to support the theory that ischaemia–reperfusion injury occurs after thrombolysis for acute leg ischaemia.

Forty patients (median age 69 years) were randomized to receive conventional low-dose thrombolysis or accelerated high-dose bolus thrombolysis with tissue-type plasminogen activator. Both groups were well matched for past medical and clinical history. Urine and blood samples were obtained before, during and after infusion. Urine was analysed to determine albumin creatinine ratios (ACR) (a marker of renal endothelial vascular permeability), and peripheral venous blood samples were analysed for serum myoglobin and malondialdehyde (MDA) levels (a product of lipid peroxidation). Statistical analysis was performed by the Mann–Whitney *U* test.

ACR levels rose significantly from baseline at 24 h in both groups (1·9 times baseline, $P = 0{\cdot}004$ for reperfusion in less than 4 h and 2·6 times baseline, $P < 0{\cdot}05$ for reperfusion after more than 4 h of thrombolysis). Patients whose infusions were completed in under 4 h had a more rapid rise in plasma MDA than those with longer infusions and the peak at 12 h was 1·5 times higher than baseline ($P < 0{\cdot}05$). Plasma myoglobin levels did not rise significantly from baseline in either group.

These results show that renal microvascular injury occurs after successful revascularization of ischaemic tissue by intra-arterial thrombolysis. Initial results suggest that the injury is not mediated by myoglobin but may be the result of free-radical activity. Free-radical scavengers and other agents that reduce reperfusion injury may therefore have a role in thrombolytic therapy.

Anatomic suitability of aortic aneurysms for endovascular repair

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Endovascular repair of aortic aneurysms using bifurcated or aortouni-iliac endoprostheses depends on anatomical suitability. This study used spiral computed tomography (CT) to assess the anatomical suitability of patients presenting electively with aortic aneurysm.

All patients underwent spiral CT scan from above the renal arteries to the common femoral arteries. Computerized reconstructions in sagittal and coronal planes and at right angles to and along the axis of the major vessels were performed and the following measurements made: aneurysm neck length and diameter, renal artery to aortic bifurcation length, common iliac artery length and diameter, and external iliac artery diameter. Patients were assessed for anatomical suitability for endovascular repair according to the authors' previously established criteria.

A total of 143 patients were studied. Thirty-one patients with aneurysm necks of less than 1·5 cm were unsuitable for repair. A further 10 patients had neck diameters of greater than 3·0 cm and were also unsuitable. Twelve further patients were rejected because of unfavourable angulation of the neck (three), aneurysm of the common iliac (five), tortuosity of the iliac vessels (three) and narrow external iliac arteries (one). This left a total of 90 patients (62·9 per cent) suitable for endovascular repair.

In conclusion, 63 per cent of aortic aneurysms greater than 4·5 cm in diameter will be suitable for endovascular repair on anatomical grounds alone.

Perioperative haemodynamics at carotid endarterectomy assessed by cerebrovascular reactivity

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Current theories about cerebral hyperperfusion following carotid endarterectomy suggest that it occurs as a result of the restoration of flow into a cerebral vascular bed in which the reactivity of blood vessels is lost because of chronic vasodilatation.

Forty-six patients undergoing unilateral carotid endarterectomy were studied using the transcranial Doppler (TCD)–carbon dioxide (CO_2) test to assess cerebrovascular reactivity before operation, and at 6, 24 and 48 h after surgery. A cerebral reactivity index (CRI) was calculated for each hemisphere. The median age of the patients was 67 (range 44–78) years. All patients had an internal carotid artery stenosis greater than 70 per cent on the operated side. The contralateral vessel was occluded in seven patients, and there was 90–99 per cent stenosis in six, 70–89 per cent in four, and less than 70 per cent in 29. Four patients showed an increase of greater than 100 per cent in the ipsilateral middle cerebral artery velocity (MCAV) within the study period.

Median MCAV on the operated side rose from a preoperative value of 45 $\mathrm{cm\,s^{-1}}$ to 62 $\mathrm{cm\,s^{-1}}$ at 6 h ($P = 0{\cdot}0001$), 64 $\mathrm{cm\,s^{-1}}$ at 24 h ($P = 0{\cdot}00001$) and 57 $\mathrm{cm\,s^{-1}}$ at 48 h ($P = 0{\cdot}0001$). The contralateral MCAV also rose from a preoperative value of 48 $\mathrm{cm\,s^{-1}}$ to 60 $\mathrm{cm\,s^{-1}}$ at 6 h ($P = 0{\cdot}008$), 57 $\mathrm{cm\,s^{-1}}$ at 24 h ($P = 0{\cdot}002$) and 59 $\mathrm{cm\,s^{-1}}$ at 48 h ($P = 0{\cdot}007$). The ipsilateral CRI rose significantly at 24 h ($P = 0{\cdot}03$) and 48 h ($P = 0{\cdot}007$), indicating a restoration of reactivity. Mean arterial pressure fell at 6 h to 89 mmHg from a preoperative value of 105 mmHg ($P = 0{\cdot}00001$) but was unchanged at other times. The ipsilateral Gosling pulsatility index increased significantly at 6 ($P = 0{\cdot}02$) and 48 h ($P = 0{\cdot}007$).

These findings indicate a restoration of cerebral reactivity by 24 h in the ipsilateral hemisphere and cast doubt on the current theory of hyperfusion. Use of the TCD-CO_2 test does not predict patients at risk of this complication.

Leukotriene inhibition does not prevent limb ischaemia–reperfusion induced gut injury

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Leukotrienes mediate portal vein neutrophil activation after limb ischaemia–reperfusion (IR). These gut-activated neutrophils may cause gut injury and promote lung damage. The leukotriene inhibitor, diethylcarbamazine (DEC), was studied to determine whether it can prevent gut injury after limb IR and whether this injury is associated with lung damage. This experiment was approved by the Home Office.

DEC (70 $\mathrm{mg\,kg^{-1}}$ loading dose then 0·7 $\mathrm{mg\,kg^{-1}\,min^{-1}}$) was started 30 min before reperfusion in one group of rats ($n = 12$) undergoing 3-h bilateral hindlimb tourniquet ischaemia and 2-h reperfusion (IR). Another IR group ($n = 12$) was treated with placebo, and a control group ($n = 10$) had placebo and 5-h anaesthesia. Lactulose and mannitol were given through a jejunostomy tube 10 min before reperfusion, and portal vein blood was assayed for lactulose and mannitol. The right lung was weighed and then dried in an oven (80°C) for 3 days. Pulmonary protein permeability was measured in bronchioalveolar lavage (BAL).

	Controls	IR and placebo	IR and DEC
Lactulose ($\mathrm{mg\,l^{-1}}$)*	5 (5–9)	88 (80–112)‡	65 (37–132)‡
Mannitol ($\mathrm{mg\,l^{-1}}$)*	5 (5–6)	61 (48–78)‡	43 (28–82)‡
Lung wet/dry ratio†	4·9 (0·03)	4·7 (0·04)	4·7 (0·03)
BAL protein ($\mathrm{pg\,l^{-1}}$)†	19·0 (4·8)	22·0 (3·8)	17·6 (2·6)

*Values are median (interquartile range); values are mean(s.e.m.). ‡$P < 0{\cdot}05$ *versus* controls (Mann–Whitney *U* test)

Increased gut permeability occurred without lung damage in moderate limb IR injury, and was not prevented by the leukotriene inhibitor.

Does soluble intercellular adhesion molecule-1 have a role in neutrophil adhesion?

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Surgical intervention for critical limb ischaemia (CLI) is associated with a high morbidity and mortality. Neutrophil (PMN) adherence to the microvascular endothelium is the initial step in diapedesis and results in the release of free radicals and proteolytic enzymes that cause tissue damage. Intercellular adhesion molecule-1 is both a cellular (endothelial) and soluble (plasma) receptor involved in PMN adherence. The authors hypothesize that soluble intercellular adhesion molecule-1 (sICAM-1) has an important physiological role in the development of ischaemia–reperfusion injury. The aim of this study was to examine PMN adhesion in patients with chronic CLI and to determine the effect of sICAM-1 on adhesion.

Blood was taken from 20 patients undergoing femoro-distal bypass for CLI (nine women, 11 men) with a median age of 72 (range 64–83) years and 15 controls (seven women, eight men) with a median age of 67 (range 54–75) years. PMN adhesion was measured by both a gelatin-based adhesion assay and adhesion to a monolayer of human umbilical vein endothelial cells (HUVEC). The PMNs were also incubated with various concentrations of sICAM-1 and the adhesion measured. The results are medians (interquartile range).

	sICAM-1 ($\mathrm{ng\ ml^{-1}}$)					
	0	0·4	41·5	415	4150	*P*
PMNs adhered (%)						
Control HUVEC	5·5 (4·0–9·0)*	3·1 (2·5–8·9)	6·7 (3·1–9·8)	5·6 (4·5–9·9)	7·8 (4·0–12)	NS
Leg ischaemia HUVEC	60 (33–65)*	57 (35–64)	39 (25–47)	20 (10–30)	10 (2–17)	<0·01†

*$P<0{\cdot}01$, Mann–Whitney *U* test; †Kruskal–Wallis analysis of variance. NS, not significant

Results for the gelatin assay agreed with the above. Leg ischaemia results in an increase in PMN adhesion, which may help to explain the morbidity and mortality associated with this condition. sICAM-1 decreased PMN adhesion in a dose-dependent manner in patients with leg ischaemia and this may provide insight into the physiological role of sICAM-1 in ischaemia–reperfusion.

Medial macrophages may cause arterial restenosis

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Macrophages identified within the human coronary and carotid restenotic arterial wall are thought to play an important role in restenosis by releasing mitogenic factors and activating smooth muscle cells, but their exact function in this process has not been determined. The aim of this study was to assess the macrophage contribution to arterial wall size and cell proliferation. A cholesterol diet was used to enhance macrophage recruitment.

Sixteen New Zealand White rabbits had their right common carotid artery balloon de-endothelialized and were fed cholesterol to produce experimental atheroma. Angioplasty of this artery was performed 2 weeks later. A further 16 animals underwent the same procedure but were not fed cholesterol. After 3 and 10 weeks the arteries were examined by immunohistochemistry using monoclonal antibodies against rabbit macrophage and proliferating cell nuclear antigen. Arterial wall size was measured on sections by a computerized image analysis system. Proliferation counts were estimated by two independent observers. This research was carried out with full Home Office approval.

	n	Time (wk)	Wall size (pixels)	Total proliferation count
Cholesterol	10	10	3·56 (2·16–4·57)*	
No cholesterol	10	10	0·77 (0·63–1·16)	
Cholesterol	6	3		258 (26–488)†
No cholesterol	6	3		62·5 (48–245)

Values are median (range). *$P=0{\cdot}001$; †$P=0{\cdot}12$ *versus* no cholesterol (Mann–Whitney *U* test)

A combination of reinjury and cholesterol feeding are required to significantly increase arterial mass and produce restenosis. Reinjury is necessary to induce medial macrophage expression which may be responsible for cell proliferation.

Smooth muscle cell culture using γ-interferon-stimulated simian virus 40 (SV40) large T antigen is feasible

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Anal continence is frequently impaired by an internal sphincter deficit. Attempts to produce an anal 'neosphincter' from smooth muscle cell culture have been complicated by difficulties in cell proliferation and identification. The first demonstration of successful smooth muscle culture using a system that drives cell proliferation in H2k mice is reported. This is a transgenic mouse that has a DNA construct, consisting of a thermolabile mutant of the simian virus 40 (SV40) large T gene driven by a promoter integrated into its genome. γ-interferon is activated by this promoter causing expression of large T which drives cells into proliferation at 33°C.

Single cells from the oesophagogastric junction, stomach, intestine, bladder and uterus were cultured using substrate attached and free-floating explants from adult and embryonic H2k mice. These were fixed and tested with anti-smooth muscle (anti-Sm M), anti-Sm M myosin, anti-Sm M α-actin, anti-caldesmon, anti-vinculin and anti-tubulin.

Results suggested that these cultured cells expressed antigens consistent with smooth muscle.

The use of γ-interferon-driven SV40 large T antigen transfected cells offers potential for smooth muscle cell proliferation. This system allows clones to be rapidly expanded in cell culture to produce the cell numbers required for construction of a neosphincter.

Anorectal and vesicourethral instability

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The bladder and rectum share a common embryological origin and parasympathetic nerve supply (S2–S4) and perform similar functions. Their interrelationship in health and disease has been established by static laboratory investigation. Combined ambulatory urodynamics and manometry studies are more physiological and may improve the detection of abnormalities.

Six patients with symptoms of urgency/urgency incontinence of micturition and defaecation were investigated by simultaneous ambulatory urodynamics and anorectal manometry and striated anal and urethral sphincter electromyography (EMG) to determine their interrelationship and whether there is a common aetiological factor. The study was approved by the local medical ethics committee.

Two Gaeltec dual sensor micro-tip pressure transducers connected to a Gaeltec MPR-2 portable recorder were placed and fixed for manometric recordings of the anal sphincter, rectal ampulla, urethral sphincter and bladder. Anal sphincter EMG was recorded by bared, hooked, fine, insulated stainless-steel wire and urethral sphincter surface EMG activity by a fine, insulated silver wire ring electrode. Patients recorded the various events by pressing an 'event marker' on the recorder and also noting these with time in the 'events diary' during the recording period. The information from the recorder was downloaded on to a personal computer.

A total of 131 h recording was obtained, with mean recording time of 21 h and 49 min per patient. A unique phenomenon of instability, simultaneously affecting the anus, rectum, bladder and urethra, was seen consistently in this group of patients. The episodes were of variable duration and occurred in the day as well as during sleep. A minimum of 10 episodes occurred in the day and seven during the night. The typical episode consisted of simultaneous rectal and vesical pressure rise (vesical and rectal contraction) and an irregular rise and fall (contraction and relaxation) of anal and urethral sphincter pressure along with corresponding EMG activity. Stronger and more prolonged episodes were associated with symptoms of urgency and urgency incontinence sometimes followed by simultaneous micturition and defaecation.

This new technique has demonstrated for the first time an instability problem in both the bladder and anorectum that appears to be responsible for the symptoms. As both striated and smooth muscle are affected the cause may be neurogenic and sited in the spinal cord.

Dynamic defaecation by stimulation of sacral nerve roots in patients with paraplegia

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Ventral sacral nerve root stimulators were developed to improve bladder emptying and to achieve continence in patients with paraplegia. However, although beneficial effects have been observed on the distal large bowel, the optimum stimulus parameters to achieve unassisted defaecation have not been determined. Bladder and anorectal function was studied during ventral sacral nerve root stimulation in patients ($n = 2$) with complete supraconal spinal cord injury. Brindley–Finetech stimulators were inserted for micturition control. The study was approved by the local medical ethics committee.

Stimulation of the nerve roots S2, S3 and S4 was performed individually and in combinations by varying the length of 'bursts' and 'gaps' of the stimulus and pulse frequency. Anorectal response to these stimuli was recorded by manometry at 2, 7 and 12 cm from the anal margin. These predetermined parameters were used during simultaneous dynamic electromyographic proctography and cystometry.

Stimulation of individual nerve roots produced a wide range of responses in anorectal pressure. S2 and S3 stimulation individually generated a rise in rectal pressure of 40–188 cmH$_2$O above basal pressure. Stimulation of S4 had little effect on rectal pressure but produced an anal pressure of up to 284 cmH$_2$O. A quick sharp fall in anal pressure was observed when the stimulus was turned off. Simultaneous stimulation of S2, S3 and S4 produced optimum rectoanal pressure gradients when stimulation was turned 'on' and 'off', but also generated high intravesical pressures of up to 99 cmH$_2$O. This intermittent stimulation produced 'periods of defaecation' during which evacuation of semisolid barium–porridge stool was seen on proctography. Stimulation patterns of bursts of 15 s with gaps of 15–20 s produce effective periods of defaecation.

Nerve roots stimulated in combination produce a better evacuation response than when roots are stimulated separately. It is equally important to stimulate the anal sphincter to its maximum as well as the rectum. Brindley–Finetech stimulators can be programmed effectively for defaecation; however the bladder should be emptied by stimulation beforehand.

Whole gut lavage: a novel method to assess pouchitis

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A novel test of gastrointestinal bleeding and protein loss based on whole gut lavage with a polyethylene glycol electrolyte solution was used to evaluate its role in pouchitis. Whole gut lavage fluid (WGLF) from 34 patients with pouches (20 men, 14 women; median age 43·5 (95 per cent confidence interval (CI) 33·5 to 53·2) years was studied. Thirteen patients had pouchitis with a pouchitis disease activity index (PDAI) of more than 7 (95 per cent CI 7 to 11) and 21 non-inflamed pouches and a PDAI of less than 7(95 per cent CI 1 to 4). Three proteins, namely immunoglobulin G (IgG), albumin and α-1-antitrypsin, were assayed by enzyme-linked immunosorbent assay and immunoturbidimetry, and haemoglobin by the Hemoquant technique. A questionnaire was completed for each patient and rigid sigmoidoscopy with biopsy was performed.

The 13 patients with active pouchitis had significantly increased levels of IgG (median 17 (95 per cent CI 7·0 to 38·0) μg ml^{-1}; $P<0·01$), albumin (27 (95 per cent CI 13·5 to 39·5) μg ml^{-1}; $P<0·003$) and α-1-antitrypsin (8 (95 per cent CI 4·5 to 11·5) μg ml^{-1}; $P<0·03$, Mann–Whitney U test) compared with levels in the non-inflamed pouches (IgG 3 (95 per cent CI 1·0 to 8·0)μg ml^{-1}, albumin 8 (95 per cent CI 6·0 to 17·0)μg ml^{-1} and α-1-antitrypsin 4 (95 per cent CI 1·0 to 7·0)μg mg l^{-1}). Haemoglobin in WGLF was similar and within the normal reference range (3 (95 per cent CI 2·5 to 5·0)μg ml^{-1} for the pouchitis group and 2 (95 per cent CI 1·0 to 5·0)μg ml^{-1} for the non-inflamed group.

In conclusion, WGLF analysis is a useful and objective means of investigating ileoanal pouches which quantifies the inflammatory effects. It is a non-invasive, well tolerated test, which enables further studies to elucidate the pathophysiology of pouchitis.

Total rectal mucosectomy preserves sensation after restorative proctocolectomy

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Restorative proctocolectomy has become the operation of choice for ulcerative colitis. The functional results, however, are imperfect and the complication rate high; there is room for improvement. The sensation of rectal distension (dependent in part on the presence of the rectum) is important in the control of defaecation. But rectal sensation is detrimentally affected following restorative proctocolectomy. A new modification of restorative proctocolectomy, conserving the whole of the rectal muscular and serosal layers, to improve perception of rectal distension and filling has been studied.

In seven patients with ulcerative colitis and one with slow transit constipation, following total colectomy, the rectum was mobilized from the pelvis, sparing the superior rectal vessels, and divided at the pelvic floor. The rectum was opened, a mucosal proctectomy was performed throughout its length, and then it was wrapped around an ileal 'J' pouch, which was stapled to the anus. A defunctioning ileostomy was raised. The patients were assessed functionally and physiologically before and after (mean 15·2 (range 8–22) months) the procedure by questionnaire, manometry and balloon distension.

The procedure was completed in six of the eight patients, being abandoned in two for difficulty in performing the mucosectomy and inaccessibility in a small pelvis. There was no postoperative mortality. Pelvic sepsis developed in two patients, both requiring operative drainage. Two patients have retained their ileostomies, one at her own request. Identical pelvic perception of rectal distension was retained both in response to the pouch filling with faeces and to artificial distension.

	n	Preop (range)	Postop (range)
24-h frequency	4	6·3 (0·14–8)	5·3 (1–10)
Continence score (maximum 55)	4	49 (40–55)	45 (33–51)
Maximum squeeze pressure (cmH_20)	6	186 (147–240)	160 (90–210)
First constant sensation (ml)	6	63 (13–160)	61 (19–150)
Desire to defaecate (ml)	6	118 (60–320)	89 (30–180)

Conservation of the rectal muscular and serosal layers maintains the sensations of rectal distension and filling and may lead to altered pouch function.

Magnetic resonance imaging of anal sphincter sepsis using an endoanal coil: pilot studies

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Magnetic resonance imaging (MRI) of perianal sepsis has variable accuracy rates; its poor local anal sphincter resolution has resulted in difficulty in localizing the primary fistulous track and its internal opening. This study has examined whether the improved MR images obtained with an endoanal coil can result in more accurate preoperative evaluation of perianal sepsis.

Ten patients with perianal sepsis (seven men; median age 38 (range 25–63) years) were studied. A cylindrical coil (diameter 9 mm, length 75 mm) was positioned endoanally and imaging performed using T1- and T2-weighted and STIR transverse images and T1-weighted coronal images after intravenous contrast. The scans were evaluated before operation by two radiologists; the consensus view was compared with the independent surgical findings.

At surgery all patients had sphincteric abscesses (intersphincteric ($n = 6$), ischiorectal ($n = 2$) and mixed ($n = 2$)). Five patients had an associated fistula *in ano* (transphincteric ($n = 2$), intersphincteric ($n = 3$)) with the internal opening at the dentate line in four.

There was concordance between MRI and surgery for the presence and site of abscesses in ten patients, the presence and site of the fistulous track in eight patients and the position of the internal opening in eight patients. At 6-months' follow-up all wounds had healed and there had been no further recrudescence of sepsis.

These data demonstrate the improved accuracy of MRI of anal sphincter sepsis using an internal coil. Further studies are necessary to confirm these preliminary findings.

Evaluation of the laparoscopic approach to total mesorectal excision

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Routine total mesorectal excision (TME) in the treatment of low rectal cancer has produced the lowest reported rates of local recurrence. In most laparoscopic-assisted anterior resections the pelvic dissection is performed during the open phase of the operation. Therefore, real doubt remains as to the ability of a pure laparoscopic rectal dissection to achieve TME. In this study all patients undergoing curative surgery with TME were studied prospectively in a non-randomized fashion. All laparoscopic procedures were performed by a single surgeon and conventional resections by a second consultant colorectal surgeon. The age, sex and median Dukes stage of the two groups were comparable. Histological examination of the resected specimens was performed by a single colorectal pathologist, blinded to the method of resection, according to standard techniques. Results are presented as median values (interquartile range).

Group (*n*)	Specimen length (cm)	Long margin (cm)	Radial margin (cm)	No. of positive margins	Lymph node yield
Laparoscopic procedure (13)	25·0 (21·1–27·6)	3·5 (2·5–4·75)	0·6 (0·3–1·15)	0	7·0 (4·8–9·8)
Open surgery (12)	28·5 (23·3–34·3))	3·0 (2·4–3·9)	1·0 (0·45–1·65)	0	10·0 (7·8–12·3)

These preliminary data confirm the technical feasibility of achieving TME performed exclusively laparoscopically, and suggest that immediate cancer clearance is not compromised. Further follow-up is required to determine the consequences of this approach on bladder and sexual function. Oncological safety will be assessed by long-term locoregional recurrence rates.

Adjuvant intraoperative photodynamic therapy for colorectal cancer

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A prospective, randomized controlled study was undertaken to determine the effect of adjuvant intraoperative photodynamic therapy (PDT) on local recurrence and survival in patients with colorectal cancer.

Control patients had the standard surgical procedure. Those in the PDT group also received photofrin 2 mg kg^{-1} intravenously and at operation the tumour bed was illuminated with 50–70-J cm^{-2} 510-nm laser light using custom-built light delivery systems.

Ninety-three patients were recruited (44 in the PDT group and 49 controls) of whom 71 were considered 'curative' (34 in the PDT group and 37 controls). Median follow-up was 3 years and 7 months (range 3 months to 5 years). No complications attributable to PDT occurred, other than mild cutaneous phototoxicity, which developed in ten patients. When all patients were included ($n = 93$) there was no difference between the two groups in survival (hazard ratio study:control (95 per cent confidence interval) 0·88 (0·44 to 1·79)). For those considered 'curative' ($n = 71$) there was no difference between the two groups in local recurrence rate (hazard ratio (95 per cent confidence interval) 0·84 (0·23 to 3·15)).

Adjuvant intraoperative PDT, at the 'dose' used in this trial, appears to be safe and well tolerated. The trial does not show a benefit in terms of survival or local recurrence, but because of its limited power at this stage a worthwhile treatment benefit has not been excluded. Recruitment of sufficient patients to prove a benefit is no longer practical using the current protocol from statistical, resource and ethical points of view. Further work, however, is justified using new second generation photosensitizers and cheaper portable more reliable light sources to replace the current laser. Such developments should make the treatment more widely available, practical and possibly more effective.

Prospective evaluation of the training and practice of a nurse flexible sigmoidoscopist

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The introduction of flexible sigmoidoscopic screening for colorectal cancer would overwhelm the medical endoscopy service. One solution is the introduction of nurse endoscopy.

This study represents the initial investigation into the results of the first nurse endoscopy service in the UK recognized by the English National Board.

The nurse was trained in four stages. Stage 1: visuospatial orientation on a colon model and observation of 35 sigmoidoscopies. Stage 2: supervised withdrawal of the sigmoidoscope in 35 patients. Stage 3: supervised performance of 35 examinations. Stage 4: independent practice with a consultant endoscopist on site but not directly supervising the procedure. Endoscopies were video-recorded and reviewed by a consultant endoscopist and every patient also underwent barium enema examination.

Eighty-seven independent flexible sigmoidoscopies have now been performed. The mean duration of the examinations was 10·5 min and the mean length of colon examined was 52·2 cm. The examination was considered incomplete in 17 patients due to discomfort ($n = 3$), inadequate preparation ($n = 9$) or stricture ($n = 5$). Thirty-eight of the completed examinations were normal. Abnormal findings comprised diverticular disease ($n = 21$), benign polyps ($n = 21$), inflammatory bowel disease ($n = 7$) and cancer ($n = 3$).

No pathology was missed by the nurse endoscopist during the period of the study.

It is concluded that, with adequate training, a nurse endoscopist is able to provide a safe and efficient flexible sigmoidoscopy service.

Laparoscopic ultrasonography for staging of gastro-oesophageal cancer

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In recent years the staging of gastric and oesophageal cancer has improved with laparoscopy and endoscopic ultrasonography (EUS). The authors' previous experience of laparoscopic ultrasonography (Lap US) with pancreatic and hepatic malignancies has demonstrated superior staging. The aim of the present study was therefore to determine the diagnostic accuracy of Lap US in staging gastric and oesophageal malignancy. Lap US, laparoscopy and computed tomography (CT) scanning were prospectively compared in the tumour node metastasis (TNM) staging of gastric and oesophageal cancer in 26 surgical candidates. Validation was by final pathology.

Resectability for potential cure was determined by Lap US with sensitivity of 100 per cent and specificity of 91 per cent *versus* 100 per cent and 73 per cent, respectively, for laparoscopy and 75 per cent and 60 per cent for CT. Overall, the accuracy of TNM staging was 82 per cent for Lap US, *versus* 67 per cent for laparoscopy and 47 per cent for CT ($\chi^2 = 8{\cdot}64$, $P < 0{\cdot}005$, and $\chi^2 = 10{\cdot}4$, $P < 0{\cdot}005$, respectively).

Accuracies for Lap US *versus* laparoscopy *versus* CT for N stage were 92 per cent *versus* 84 per cent *versus* 70 per cent, for T stage 92 per cent *versus* 42 per cent *versus* 60 per cent and for M stage 89 per cent *versus* 44 per cent *versus* 62 per cent, respectively. T and N staging by Lap US were comparable with published results using EUS and overall TNM staging was better.

Lap US may provide the optimal preoperative staging for gastric cancer and may complement EUS in staging oesophageal cancer. This may have implications for neoadjuvant therapy protocols and for selecting patients for non-operative palliation.

Comparison of immunological and physiological effects of carbon dioxide pneumoperitoneum at room and body temperatures

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Prolonged and complex laparoscopic procedures predispose patients to large volumes of cool insufflation gas. The aim of this study was to compare the effects of a conventional room temperature carbon dioxide (CO_2) pneumoperitoneum with those of a body temperature pneumoperitoneum. The physiological and immunological effects of warming the gas were examined by measuring peroperative core and intraperitoneal temperatures, peritoneal fluid cytokine concentrations, postoperative pain and inflammatory changes in peritoneal biopsy specimens.

Patients were randomized to undergo laparoscopic cholecystectomy with a CO_2 pneumoperitoneum warmed to either body temperature ($n = 15$) or room temperature ($n = 15$). The mean duration of surgery was 32 min in both groups. Core temperature was reduced in patients with room temperature pneumoperitoneum (median 0·42°C; $P < 0{\cdot}05$). There was no reduction in temperature when the gas was warmed. Greater levels of cytokines were detected in the peritoneal fluid of patients with room temperature pneumoperitoneum (tumour necrosis factor: median value 10·9 *versus* 0·42 pg ml^{-1}, $P < 0{\cdot}05$; interleukin 1: 44·8 *versus* 15·5 pg ml^{-1}, $P < 0{\cdot}05$; interleukin 6: 60·4 *versus* 47·2 ng ml^{-1}). There was no difference in postoperative pain scores or analgesia consumption between the two groups. Histological examination of peritoneal biopsy specimens showed greater inflammation scores at the end of surgery than the start ($P < 0{\cdot}05$), but temperature of the insufflation gas did not affect the degree of peritoneal inflammation.

Intraoperative hypothermia can be prevented by warming insufflation gas, even in short laparoscopic procedures. In addition, warming the insufflation gas leads to a reduced postoperative intraperitoneal cytokine response.

Effect of intra-abdominal pressure on pain and pulmonary function after laparoscopic cholecystectomy

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The mechanisms of pain and depressed pulmonary function after laparoscopic cholecystectomy are poorly understood. The aim of this study was to examine the effect of a carbon dioxide pneumoperitoneum at different intra-abdominal pressures on pain and pulmonary function after laparoscopic cholecystectomy.

Forty patients with symptomatic gallstones were randomized to laparoscopic cholecystectomy at intra-abdominal pressures of either 7·5 (group 1) or 15 cmH$_2$O (group 2). Patients in both groups were similar with respect to age, sex, American Society of Anesthesiologists grade, body mass index and biliary symptom scores.

Group	No. of patients	Pain* 6 h	Pain* 24 h	PEFR at 24 h†	Hospital stay (days)
1	20	56 (47–76)	46 (28–62)	68 (53–88)	1·5 (1–2)
2	20	87 (77–104)	95 (36–114)	53 (39–66)	2·0 (2–3)
P		0·04	0·01	0·04	0·01

Values are median (interquartile range). *Percentage of biliary symptom scores. † Percentage of preoperative levels. PEFR, peak expiratory flow rate

Insufflation time 41 *versus* 37 min and operating times 51 *versus* 52 min were similar for both groups. This study demonstrates that intra-abdominal pressure has a significant effect of postoperative pain and pulmonary function and should be taken into consideration when performing laparoscopic cholecystectomy.

Fibrinogen concentrations are increased in advanced oesophageal carcinoma: implications for thromboembolism prophylaxis

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Since the description of thrombophlebitis migrans in association with gastric carcinoma by Trousseau in 1865, hypercoagulability is a well recognized phenomenon associated with malignancy and results in an increased risk of thrombosis during surgery. In this prospective study fibrinogen concentrations were measured before operation in a consecutive series of 65 patients undergoing surgery for oesophageal carcinoma. A pro forma detailing presenting complaints, clinical findings and an accurate smoking history was completed before surgery. All patients had a thorough preoperative investigation which included routine blood tests, pulmonary function tests, ultrasonography and computed tomographic scan of the chest and abdomen. Patients were staged according to standard Union Internacional Contra la Cancrum criteria.

Fibrinogen concentrations were significantly higher in patients with malignancy than age- and sex-matched control patients with benign disease and fibrinogen concentrations increased with more advanced disease. Patients with stage IV disease were significantly younger and had significantly higher bilirubin levels than patients with less advanced disease. There were trends towards higher cigarette consumption, greater weight loss, lower albumin levels and increased liver function tests in patients with stage IV disease, but the differences were not significant.

	Benign	Stage I	Stage II	Stage III	Stage IV	*P**
No. of patients	23	7	12	36	10	
Fibrinogen (mg/ml)	3·0 (1·0)	3·7 (1·5)	4·6 (1·5)	5·3 (1·2)	7·4 (1·8)	< 0·001
Age (years)	66·8 (2·3)	68·8 (2·9)	66·7 (2·1)	66·9 (1·3)	58·0 (5·1)	< 0·05
Bilirubin (mg/ml)		10 (1·5)	10 (1·3)	10 (0·9)	73·2 (20·8)	

Values are mean(s.e.m.). *Analysis of variance

This association between advancing stage of disease and fibrinogen concentration in patients presenting with oesophageal carcinoma has implications for prophylaxis against venous thromboembolism.

Comparison of c-*met* protein expression in intestinal and diffuse gastric cancer from Britain and Japan

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The hepatocyte growth factor receptor c-*met* has mitogenic, motogenic and morphogenic properties, and has been implicated in the development of gastric cancer. Amplification, mutation or RNA overexpression for the c-*met* gene reportedly occurs more frequently in well differentiated 'intestinal' than in poorly differentiated 'diffuse' type cancers, but c-*met* protein distribution has not previously been reported. Expression of c-*met* protein in 40 British and 20 Japanese tumours was studied by immunohistochemistry. Twenty-seven tumours were diffuse, 21 intestinal and 12 of indeterminate morphology. Snap-frozen tissue sections were stained by the APAAP technique, using a monoclonal c-*met* antibody. Staining was recorded on a four point scale (0 to + + +).

Intestinal tumours showed prominent luminal and basolateral c-*met* staining. Diffuse tumours showed a less structured staining distribution. Nineteen diffuse and 18 intestinal tumours showed strong c-*met* expression (+ + or + + +) ($\chi^2 = 0\cdot825$, $P = 0\cdot36$). The frequency of strong c-*met* protein expression was similar in the British (77 per cent) and Japanese (85 per cent) populations.

High levels of c-*met* protein expression were found in both diffuse and intestinal-type cancers.

These findings do not support an important role for c-*met* in defining the morphological type of gastric cancer. No biological difference was noted between British and Japanese gastric cancer in relation to c-*met* expression.

Helicobacter pylori-induced platelet aggregation *in vivo* in the gastric mucosal microcirculation of the rat

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The exact mechanisms by which *Helicobacter pylori* infection results in gastric mucosal injury are unclear. The aim of this study was to directly assess *in vivo* whether *H. pylori* extracts could initiate an inflammatory response in the rat gastric mucosal microcirculation.

Animals were anaesthetized with hypnorm and diazepam (1 : 1 ratio) and an incision was made in the exteriorized stomach. Extracts of *H. pylori*, *Escherichia coli*, or distilled water were administered topically to the gastric mucosa. Fluorescent *in vivo* microscopy was used to assess macromolecular leakage of fluorescein-labelled albumin from mucosal vessels and to study leucocyte and platelet activity for 90 min. Experiments were carried out with Home Office approval.

H. pylori extracts induced an 11 per cent increase ($P < 0\cdot02$) in albumin leakage after only 5 min. This decreased to values seen with *E. coli* and distilled water. Significant increases ($P < 0\cdot001$) in both adherent platelet thrombi as well as circulating platelet emboli were observed after 5 and 15 min, respectively. Adherent platelet thrombi (mean of four per field of view) remained significantly increased throughout the experiment, but circulating emboli (maximum of five at 30 min) decreased with time. All observations were unique to *H. pylori*. Significant changes in leucocyte adherence were not observed.

This is the first *in vivo* study to demonstrate the ability of *H. pylori* extracts to promote platelet aggregation within gastric mucosal microvessels. Recruitment of leucocytes was not observed. The results suggest that the early events associated with *H. pylori* infection are platelet aggregation with perhaps subsequent leucocyte recruitment by activated platelets.

Total antioxidant capacity in acute pancreatitis

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Acinar cell injury in acute pancreatitis leads to an increased production of oxygen free radicals (OFRs). These may play an important role in acute pancreatitis by increasing capillary permeability, leading to local and distant tissue damage.

OFRs are scavenged by intracellular antioxidants and serum factors, principally albumin, urate, ascorbate, α-tocopherol and retinol. A balance normally exists between the serum total antioxidant capacity (TAC) and OFR. Potential for damage arises when the production of OFRs rises beyond the TAC.

TAC in 23 patients with acute pancreatitis was measured by colorimetry on admission and daily for 5 days. Serum albumin and urate were also measured as components of TAC. A control group consisted of 22 patients undergoing elective surgery.

TAC was significantly lower in patients with pancreatitis than in controls before surgery, both on admission (median 1·4 (interquartile range (IQR) 1·3–1·6) *versus* 1·6 (IQR 1·4–1·8) mmol l^{-1}, $P = 0\cdot016$) and the day of the lowest measurement (1·3 (IQR 1·2–1·4) *versus* 1·6 mmol l^{-1}, $P = 0\cdot0001$, Mann–Whitney *U* test, day 3). Both albumin (34 (IQR 31–37) *versus* 37 (IQR 34–41) g l^{-1}, $P = 0\cdot017$, day 1; 31 (IQR 25–35) *versus* 37 g l^{-1}, $P = 0\cdot0033$, day 3) and urate (243 (IQR 197–266) *versus* 381 (IQR 308–446) μmol l^{-1}, $P = 0\cdot0001$, day 1; 210 (IQR 192–281) *versus* 381 μmol l^{-1}, $P < 0\cdot0001$, day 3) were also lower in patients with pancreatitis than in controls.

These results indicate that serum TAC is reduced in acute pancreatitis. This may be a non-specific reduction caused by loss or dilution of the major component factors, albumin and urate. Nevertheless, serum TAC in acute pancreatitis may be unable to counterbalance increased OFR production, resulting in organ damage. If low levels of TAC are found to correlate with organ damage, then its measurement may permit the identification of patients who might subsequently benefit from antioxidant therapy.

Differential densities of nitrergic nerves in sphincteric and non-sphincteric smooth muscles of fetal gut

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Nitric oxide is involved in the inhibitory neurotransmission of gut. However, the relative contribution of nitrergic innervation to the functionally diverse sphincteric and non-sphincteric regions is unknown.

The densities of nitrergic nerves in gastrointestinal sphincters and adjoining non-sphincteric bowel were studied in 14 fetuses with a computerized image analysing system on reduced nicotinamide adenine dinucleotide phosphate diaphorase-stained sections.

Results are given as mean (s.e.m.) nitrergic nerve : muscle areas in percentages

	Nitrergic nerve density at fetal age (weeks)			
	12–13	14–15	16–17	23
Lower oesophageal sphincter	11·8(0·6)	9·4(0·6)	7·1(1·0)	3·5(0·2)
Stomach	12·2(0·9)	8·6(0·7)	8·2(0·6)	5·6(0·5)
Pylorus	8·4(0·8)	5·8(0·8)	4·7(0·5)	3·0(0·4)
Rectum	24·8(0·7)	18·2(0·6)	14·7(0·7)	8·4(0·5)
Internal anal sphincter			9·6(0·6)	4·6(0·3)

In summary, nitrergic nerve densities of gut muscles decrease progressively during development as a result of increased spacing of ganglia and disproportionately greater increase in muscle volume. The effect is particularly pronounced in sphincters where the precarious neurone : muscle ratios may explain their susceptibility to dysmotility disorders.

Stimulation of T lymphocyte function in a rodent model of colorectal cancer by L-arginine

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The authors have previously reported an inhibiting effect of L-arginine on colonic carcinogenesis induced by 1, 2-dimethylhydrazine (DMH). The aim of this study was to investigate the mechanism of action of arginine involved in this model. The authors hypothesized that dietary supplemental arginine would modulate host lymphocyte immune function in colorectal cancer.

Male Wistar rats were treated with weekly subcutaneous injections of DMH (20 mg per kg body weight) or ethylene diamine tetra-acetic acid (EDTA) (as a DMH vehicle solution) for 20 weeks. Arginine was given in a 1 per cent solution of drinking water. Animals were divided into four groups: group I was given EDTA; group 2 EDTA and arginine; group 3 DMH; and group 4 DMH and arginine. Lymphocyte proliferative response to T cell mitogen (PHA, 50 μg ml^{-1}) was determined using the uptake of tritiated thymidine and T lymphocyte subsets (CD2, CD4 and CD8) were assessed by flow cytometry.

Lymphocyte proliferative response to PHA significantly increased in both groups of animals receiving arginine compared with those given EDTA and DMH ($P < 0\cdot05$, Mann–Whitney U test). Total T lymphocytes (CD2) and helper T cells (CD4) increased in both arginine-treated groups ($P < 0\cdot05$), but the ratio of CD4/CD8 remained the same. Fourteen of 18 animals given DMH developed colonic tumours compared with nine of 17 that received arginine. No tumour was found in groups 1 and 2.

Dietary supplemental arginine significantly enhanced T lymphocyte response to PHA and total T lymphocyte distribution. The beneficial effect of arginine on carcinogenesis of this colorectal cancer model appeared, at least in part, to be 'no specific' stimulation of the host immune system.

Relationship between p53 protein accumulation and gene mutations

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Genetic abnormalities in p53 and accumulation of p53 protein are frequently found in human cancers and may have prognostic significance. Recent evidence suggests that mechanisms other than gene mutation can cause p53 accumulation. The aim of this study was to (i) quantitate p53 protein expression in tumour cells by flow cytometry (FCM), Western blotting and immunocytochemistry (ICC); and (ii) study the effectiveness of different antibodies in measuring p53 content and in detecting mutations.

Thirteen cultured tumour cell lines were assessed for p53 content by FCM and ICC using antibodies NCL-p53-DO7, NCL-p53-240, NCL-p53-1801 and NCL-p53-CM1. Five tumour cell lines were sequenced in commonly mutated regions of the p53 gene (exons four to nine) and analysed by FCM and Western blotting.

FCM for p53 content gave reproducible results with little intraobserver variation ($r = 0\cdot997$, Pearson's correlation coefficient; $P < 0\cdot001$) or interobserver variation ($r = 0\cdot924$; $P < 0\cdot001$). FCM correlated with ICC for staining intensity and per cent positivity for DO-7, 240 and 1801 ($P < 0\cdot001$ to $P < 0\cdot02$) but not for the polyclonal antibody, CM1. In the absence of gene mutation, FCM assessment was consistent with Western blotting for the monoclonal antibodies but not for CM1. Using FCM and Western blotting, DO-7, 240 and 1801 detected p53 protein in both mutated and non-mutated cell lines; staining intensity was strongest for DO-7 and least for 240 in non-mutated cell lines. In mutated cell lines, FCM assessment using DO-7 again detected more p53 protein than 240 or 1801 ($P = 0\cdot05$).

In conclusion, the FCM detection of p53 protein in cells is rapid, reproducible and quantitative. p53 accumulation is not synonymous with gene mutation.

Role of ezrin in hepatocyte growth factor/scatter factor-induced membrane ruffling

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Membrane ruffling of tumour cells is correlated with motility and metastatic potential. This study examined the role of ezrin, a membrane-cytoskeleton linker protein, in tumour cell membrane ruffling induced by hepatocyte growth factor/scatter factor, a tumour invasion promoter.

Membrane ruffling of the human colon cancer cell, HT115, was monitored by time-lapse video recording and scanning electron microscopy. Expression of ezrin and its tyrosine phosphorylation in the cell were determined by immunoprecipitation and Western blotting. Its cellular location was visualized by indirect immunofluorescence.

Hepatocyte growth factor/scatter factor induced vigorous membrane ruffling which appeared as early as 5 min (ruffling index 0·55 (0·08) *versus* 0·20 (0·03) in controls, $P<0{\cdot}05$ Mann–Whitney U test) and reached a maximum in 30 min (ruffling index 1·42 (0·06) *versus* 0·20 (0·03) in controls, $P<0{\cdot}01$). This was related to increased cell motility (increased colony scattering and cell–cell dissociation). Hepatocyte growth factor/scatter factor also induced rapid tyrosine phosphorylation of ezrin. Immunofluorescent staining revealed translocation of ezrin from cytoplasm and generalized cell surface to discrete areas of polarized ruffled membrane.

Ezrin plays a key role in hepatocyte growth factor/scatter factor-induced cellular membrane ruffling and may present an important step in tumour metastasis.

Eicosapentaenoic acid-induced apoptosis *in vitro* is attachment dependent

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The authors have previously shown that eicosapentaenoic acid (EPA) inhibits proliferation of the pancreatic cancer cell line MIA PaCa-2 by cell cycle arrest and induction of apoptosis *in vitro*. Membrane function and interaction with substrate may play a key role in these effects. The aim of this study was to investigate the effect of cell attachment on EPA-induced cell cycle arrest and apoptosis *in vitro*.

MIA PaCa-2 cells were cultured in medium with or without EPA supplementation (50 μmol l^{-1} in uncoated culture wells or wells coated with poly(2-hydroxyethyl methacrylate) (poly (HEMA)). Poly(HEMA) prevents MIA PaCa-2 cells from attaching to the plastic surface. The cells were harvested after 72 h incubation. The cell count, cell cycle distribution and percentage of cells in the sub-G1 phase were determined.

MIA PaCa-2 grew as an adherent monolayer in plastic wells but as non-adherent clumps in poly(HEMA)-coated wells. In uncoated wells, there was a reduced cell count and a substantial sub-G1 peak when cells were grown in the presence of EPA. In poly(HEMA)-coated wells, there was no difference in either cell count or cell cycle distribution between cells grown in the absence or presence of EPA.

	Uncoated culture wells		Poly(HEMA)-coated wells	
	No EPA	EPA (50 μmol l^{-1})	No EPA	EPA (50 μmol l^{-1})
Cell count	2586 (103)	387 (21)*	2600 (149)	2465 (159)
Sub-G1 (%)	1·6 (0·3)	23·3 (1·1)*	1·2 (0·1)	1·4 (0·1)

Values are mean (s.e.m.) $^{*}P<0{\cdot}001$ *versus* no EPA (Student's paired t test)

MIA PaCa-2 cells were protected against the induction of cell cycle arrest and apoptosis by EPA when they were denied attachment to a plastic surface. This observation suggests that signals derived from substrate attachment are essential for the process of EPA-induced apoptosis.

Tumour cell adhesion to extracellular matrix and phosphorylation of focal adhesion kinase induced by hepatocyte growth factor/scatter factor

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Tumour cell adhesion to extracellular matrix (ECM) is a key step in the establishment of distant metastases. This study examined the regulation of adhesion of tumour cells by hepatocyte growth factor/scatter factor (HGF/SF) to ECM and the role of focal adhesion kinase (FAK), a molecule for the signal transduction of integrin-mediated cell matrix adhesion.

Human breast cancer cells MDA MB 231 and colon cancer cells HT115 were used. Tumour cells were pretreated with HGF/SF in a range of concentrations for various periods. Cell adhesion to ECM (Matrigel) was determined by Hoechst 33528 assay. Levels of $\beta 1$, $\alpha 3$, and $\alpha 5$ integrins and FAK were determined by Western blotting and their cellular location visualized by indirect immunofluorescence.

Pretreatment with HGF/SF (over 10 min) significantly increased cell adhesion to Matrigel for both cell types (mean(s.d.) 61·0 (0·5) *versus* 49·6 (3·2) per cent in controls with MDA MB 231, 53·1 (1·3) *versus* 40·4 (5·6) per cent with HT115, $P<0{\cdot}05$, Mann–Whitney U test). This occurred in a time-dependent manner. Both cells expressed $\beta 1$, $\alpha 3$, and $\alpha 5$ integrins, and FAK. Tyrosine phosphorylation of FAK was increased by HGF/SF. Indirect immunofluorescence revealed that HGF/SF induced a marked FAK-containing focal adhesion complex.

HGF/SF increases tumour cell adhesion to extracellular matrix by activation of FAK. This may be important in understanding the interactions between tumour cells and extracellular matrix.

Keratinocyte growth factor is a paracrine agent in the human prostate gland

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Keratinocyte growth factor (KGF) or fibroblast growth factor-7 (FGF-7) has been identified as a peptide paracrine growth factor in the mouse. Data confirming its potential role as a paracrine factor in human prostate cancer are reported here. A series of snap-frozen prostate cancer specimens were studied, along with primary cultured epithelial and stromal cells obtained from normal, benign hyperplastic and malignant prostates. KGF gene expression was detected using reverse transcription-polymerase chain reaction (RT-PCR). Integrity of RNA was confirmed by RT-PCR of a house-keeping gene, glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Sixteen tumours were included (six poorly differentiated, six moderately differentiated and four well differentiated). Seven tumour samples expressed KGF transcript. The cell type responsible for this expression was investigated using a primary culture model. KGF mRNA was found in prostatic stromal cells from normal, benign hyperplastic and malignant prostates, but it was not found in prostatic epithelial cells.

Certain specific splice variants of the FGF receptors (tyrosine kinase receptors) had preferential binding for KGF. The expression of such receptor variants in prostatic epithelium was identified using RT-PCR.

In conclusion, data support the potential role of KGF as a paracrine factor in the prostate gland, with the peptide expressed in stroma and its receptor in epithelium.

Quantitation of c-*erbB*2 expression in human breast cancer with correlation to gene amplification

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Amplification of the c-*erbB*2 oncogene predicts poor outcome in breast cancer. The authors have developed a quantitative radio-immunohistochemical (R-ihc) method for measuring this receptor. Eighty-one tumours were studied of which 90 per cent overexpressed c-*erbB2*. This is considerably higher than the reported rate of gene amplification. In addition, this technique clearly demonstrates a bimodal distribution of c-*erbB2* expression. The table shows the characteristics of these modes.

R-ihc	*n* (%)	Mean log B-2	95% CI
Controls	8 (—)	1·00	0·86–1·14
Mode 1	64 (79)*	2·49	2·41–2·57
Mode 2	17 (21)	4·27	4·14–4·40

Values of c-*erbB2* are expressed as a percentage of the mean of normals and then log transformed (log B-2). Reduction mammoplasty tissue was used as a control. *$P<0·0005$, analysis of variance; CI, confidence interval.

Fluorescent *in situ* hybridization (FISH) studies on 29 of these tumours shows gene amplification is responsible for the second frequency peak.

FISH	*n*	Mean log B-2	95% CI
Unamplified	15	2·56	2·39–2·73
Amplified	14	4·17	3·91–3·43

$P<0·0005$, analysis of variance

Conventional assays identify the second peak, however expression within the first mode is up to 20 times that of normal.

Application of this assay to a larger group of tumours will allow assessment of whether these lower levels of expression are of functional significance.

Pattern of expression of metastasis-associated genes in breast cancer resected during various menstrual phases

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Several retrospective studies have demonstrated significant improvement in survival among women with breast cancer resected during the luteal phase of their menstrual cycle. A pilot study of 30 premenopausal women with early breast cancer was conducted to explore the possible mechanism for this phenomenon. The study included hormonal monitoring, to define accurately the menstrual phase during which surgery was carried out. The authors hypothesize that unopposed circulating oestrogen is responsible for the adverse effects of performing surgery during the follicular phase and that the presence of progesterone during the luteal phase may mitigate this effect.

The patterns of expression of metastasis-associated genes and their inhibitors that may be hormonally regulated were assessed using Northern blot analysis of RNA from fresh tumour specimens. Preliminary results show increased expression of cathepsins L and D, and 92 KDa and 72 KDa collagenases (*t*-test = 0·005, 0·10, 0·07, 0·26) and decreased expression of their inhibitors TIMP-1 and TIMP-2 (*t*-test = 0·12, 0·19) in tumours resected during the follicular phase compared with those resected in the luteal phase.

Larger prospective studies are needed to determine the possible effect of these findings on long-term survival.

Is overexpression of the parathyroid hormone-related protein receptor a predisposing factor in bone metastasis from breast cancer?

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Parathyroid hormone-related protein (PTHrP), an osteolytic factor secreted by osteoblasts and tumour cells, predisposes to bone metastasis. Recently, the receptor for PTHrP was cloned and its expression in breast cancer has been studied here to determine its role in the development of bone metastases.

In situ hybridization was used to identify the cellular location of the receptor for PTHrP in early breast carcinoma ($n=107$), normal breast tissue ($n=12$) and bone metastases ($n=28$). The complementary DNA probe was labelled with ^{35}S and control slides treated with crude ribonuclease. Tumours were scored by two independent observers using the product of intensity of signal (1–3) and the number of positive tumour cells (1 < 20 per cent, 2 > 20 per cent and < 80 per cent, 3 > 80 per cent). A score of six or more defines overexpression of the PTHrP receptor.

Normal ductular epithelium expressed messenger RNA for the PTHrP receptor (median score 3 (range 1–3)). Hyperplastic epithelium was strongly positive with a median score of 6 (range 2–6).

	PTHrP receptor levels		
	Overexpressed	Normal	Absent
Primary breast carcinoma	49 (46)	50 (47)	8 (7)
Bone metastases	20 (71)	8 (29)	0

Values in parentheses are percentages

Primary breast cancer expressed the PTHrP receptor but the signal intensity in bone metastases was significantly higher (median score 6 *versus* 3, $P<0·001$). The level of expression of the receptor within primary breast carcinoma did not relate to any known prognostic factors.

Overexpression of the PTHrP receptor in breast cancer bone metastases implies that autocrine/paracrine growth stimulation by PTHrP predisposes to skeletal spread in breast carcinoma.

Growth factor receptor expression is not a prognostic indicator in young patients with colorectal cancer

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Colorectal cancer in the under-45 age group comprises approximately 3 per cent of all cases. Dukes staging is an important factor determining survival in these patients. Recently, growth factor receptor expression has been shown to be of prognostic significance in certain cancers but its prognostic role in young patients with colorectal cancer has not been evaluated. The aim of this study, therefore, was to determine prognostic factors, in particular, growth factor receptor expression (c-*erb*B2, epidermal growth factor receptor (EGFR) and transforming growth factor β receptor (TGFβR)), in such patients.

Ninety-one patients (44 males and 47 females) 35 with rectal and 56 colonic tumours, were evaluated. These were staged using tumour node metastasis, Dukes and Jass classifications, and examined with reference to overall survival. Formalin-fixed, wax-embedded material (tumour and regional nodes) was examined microscopically for evidence of extramural vascular invasion, and expression of c-*erb*B2, EGFR and TGFβR using a streptavidin–biotin immunohistochemical technique. The percentage of cells expressing each receptor was evaluated.

The Cox stepwise regression model was used to perform multivariate analyses, evaluating the significance of these factors as independent prognostic variables. Independent risk factors for overall survival were: nodal status ($P<0{\cdot}01$), metastases at diagnosis ($P<0{\cdot}01$) and presence of extramural vascular invasion by tumour ($P<0{\cdot}006$). However, expression of c-*erb*B2, EGFR and TGFβR were not independent prognostic factors for survival.

This study has identified that extramural vascular invasion by tumour, but not expression of growth factor receptors, is an important prognostic indicator in young patients with colorectal cancer. This may have implications in the selection of patients for adjuvant therapy after curative surgery.

Expression of activated gelatinase A is increased in colorectal cancer

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The matrix metalloproteinases are overexpressed in certain types of cancers. Gelatinase A (72 kDa gelatinase) has the tightest correlation with tumour invasion and metastasis and this may be the result of its ability, when activated, to breakdown the basement membrane. Gelatinase A can be measured by a variety of techniques but gelatin zymography is the only technique that can differentiate between the active 62 kDa form and the inactive 72 kDa proenzyme.

Zymography of 58 known concentrations of pure gelatinase showed that, using computerized image analysis, the technique was quantitative within the 0–50 ng range ($r=0{\cdot}813$) with a linear relationship. The main source of error was intergel variation; the authors were able to correct this variation using their standard curve and known standards of all gels.

Gelatinase expression in 13 freshly frozen colorectal cancer specimens and their corresponding normal control samples was studied using this technique. Four separate samples were obtained for each tissue sample and zymography performed. Each value was corrected for intergel variation and calculated per mg protein. There was overexpression of gelatinase in the colorectal tumour samples compared with that in the normal control specimens (92 kDa gelatinase ($P<0{\cdot}0005$), 72 kDa gelatinase ($P<0{\cdot}05$) and the active 62 kDa gelatinase ($P<0{\cdot}001$, paired Student's t-test)).

In conclusion, zymography is a useful and quantitative technique to detect gelatinase expression. Active 62 kDa gelatinase is tightly correlated with the malignant phenotype.

Endogenous interleukin 2 receptor correlates with the quality of life in patients with colorectal liver metastases

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The authors have previously suggested that circulating colorectal liver metastases (CLM) products could affect quality of life (QOL). In this study, circulating serum levels of immune products (tumour necrosis factor receptor 1 (TNFR1), interleukin 2 receptor (IL-2R), interleukin 6 (IL-6)) were correlated with tumour volume and QOL in 44 patients with CLM. Immune products were measured by an enzyme-linked immunosorbent assay method and tumour volume (ml) was calculated from computed tomography. QOL was measured using standard instruments (Rotterdam symptom checklist (RSC), hospital anxiety and depression scale (HAD scale), sickness impact profile (SIP)).

Abnormal increases in serum TNFR1, IL-2R or IL-6 were detected in 40 patients. There was a significant positive correlation between serum IL-2R and the HAD scale depression ($r=0{\cdot}7$, $P<0{\cdot}0001$), RSC ($r=0{\cdot}5$, $P<0{\cdot}01$) and SIP ($r=0{\cdot}5$, $P=0{\cdot}009$) scores, and tumour volume ($r=0{\cdot}5$, $P<0{\cdot}0009$). There were no significant correlations with serum TNFR1 or IL-6 levels. Regression analysis comparing tumour volume, serum alkaline phosphatase, serum carcinoembryonic antigen and immune product levels as the independent variable selected serum IL-2R as the strongest predictor of the RSC physical symptoms score ($P<0{\cdot}03$).

This is the first demonstration of a correlation between QOL and serum immune product levels in patients with cancer, and supports the hypothesis that circulating tumour products may affect QOL in patients with CLM.

Reverse transcriptase polymerase chain reaction coding for carcinoembryonic antigen complementary DNA in blood can identify circulating colorectal cancer cells

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Although metastasis is thought to occur by blood-borne dissemination, there have been few demonstrations of viable circulating cancer cells in patients with malignant tumours. There have been attempts to use reverse transcriptase polymerase chain reaction (RT-PCR) to identify circulating tumour cells in breast and colorectal cancer by amplifying complementary DNA (cDNA) coding for cytokeratins expressed by normal epithelial cells. RT-PCR was used to identify cDNA coding for carcinoembryonic antigen (CEA) in patients with primary colon cancer, colorectal liver metastases and control patients with no known malignant disease.

Southern blot hybridization confirmed the presence of CEA cDNA using a specific oligoprobe, the sequence of which lies between the two primers used. Spiking control blood with the CEA-producing HCT115 colorectal carcinoma cell line suggested a detection threshold of ten CEA-producing cells per ml blood.

There was a significant increase ($P<0{\cdot}02$) in the prevalence of expression of CEA cDNA in patients with colorectal cancer (32 of 61, 52 per cent) compared with controls (five of 22), but no significant difference between patients with liver metastases (28 of 52, 54 per cent) and those with primary colorectal cancer (four of nine, 44 per cent) There was no significant association between the prevalence of RT-PCR cDNA expression and tumour volume determined by CT or serum CEA level in patients with liver metastases.

This is the first demonstration of the potential for RT-PCR to identify circulating CEA-expressing cells. The technique is sensitive and may be useful in staging colorectal cancer but the reason for positive results in controls is yet to be determined.

Sensitive flow cytometric method for the detection of oestrogen, progesterone and epidermal growth factor receptors in gastric cancer

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Increased expression of receptors for the sex hormones oestrogen (ER) and progesterone (PR) and for epidermal growth factor (EGFR) have been reported in gastric adenocarcinoma (GC) and are thought to be associated with cell proliferation in neoplastic as well as normal gastric epithelium. Most studies of tumours have used immunohistochemistry to determine expression, with results showing 0–64 per cent positivity for ER, 9–72 per cent for PR and 35–69 per cent EGFR. The aim of this prospective study was to quantify accurately the expression of these receptors on GC cells by flow cytometry and to assess their relationship to well established prognostic indicators.

Fluorescein isothiocyanate-conjugated cytokeratin-positive gated cells stained with biotin–streptavidin phycoerythrin-conjugated monoclonal antibodies specific to the receptors (NCL-PGR for PR, NCL-R1 for EGFR) or their associated protein (ER-1D5 for ER) were analysed by flow cytometry and their expression determined as median fluorescent values. These were expressed as molecules of equivalent soluble phycoerythrin. Tumour biopsy specimens were analysed from 50 patients with GC: ten biopsy specimens from normal stomachs served as controls. Mann–Whitney *U* and Spearman's correlation tests were used to determine significance and correlation.

The mean (s.e.m.) age of the patients was 67·9 (1·23) years and 32 were male. There was no significant association between expression of any receptor and the sex or age of the patients studied. ER was expressed in 74 per cent of tumours and 40 per cent of controls ($P<0\cdot05$). PR was found in 94 per cent of tumours and 100 per cent of controls (not significant). EGFR was expressed in 86 per cent of tumours and 50 per cent of controls ($P<0\cdot05$). There were no significant associations between receptor status and known prognostic indicators such as grade, nodal status or T stage of the tumours. Significant positive correlations were found between expression of ER and EGFR ($P<0\cdot05$) and PR and EGFR ($P<0\cdot05$). There was however no correlation between expression of ER and PR.

These results show increased expression of ER and EGFR in GC and strong correlation between sex hormone expression and EGFR. There were also more receptor-positive patients in this study than in data published to date. The authors believe that this is related to the sensitivity of the flow cytometric assay being able to detect low levels of expression of the receptors.

Evaluation of functional multidrug resistance in primary urothelial cancer explants by confocal microscopy

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Assessing functional multidrug resistance (MDR) status to anthracyclines in clinical biopsy material using drug autofluorescence has potential applications for management. The recent proliferation of MDR markers increases the attractiveness of simple functional assays of drug uptake and intracellular partition. The small size of many biopsy specimens has led the authors to develop a protocol for studying drug accumulation in adherent explanted primary cancer cell colonies viewed live and *in situ* by confocal microscopy.

Explants from 22 of 23 patients with bladder tumours at varying stages of treatment developed epithelial skirts within a few days of culture in McCoys 5A medium on gelatin-coated Petri dishes. These were exposed for 1–2 h to epirubicin 10 μg ml^{-1} and examined directly under water immersion lenses by a point-scanning confocal system. Drug uptake and partition were compared with normal and P-170 positive adriamycin resistant clones of a urothelial cell line.

Classical patterns of sensitive and resistant drug distribution were observed, including colonies with mixed populations in four of five cases where clinical resistance might be inferred. Cells of the rolled edges of larger colonies accumulated more drug than those of the more central epithelial monolayer. Penetration of the phospholipid analogue PKH2-GL also showed the edge effect, but not of the viability marker, fluorescein diacetate. Scoring a colony with a soft instrument evoked an edge effect at the new artificial margins. Some central areas of larger colonies gave the novel appearance of drug arrested at cell junctions.

These observations contribute to the understanding of mechanisms in MDR and form the basis for a clinical MDR evaluation protocol. Variations in drug handling by organized live cells have implications for the interpretation of flow cytometric studies, where all cells are likely to show more uniform fluorescence corresponding to peripheral cells in colonies. Equally, clinicians might consider strategies to abrogate the reduced uptake illustrated by central cells of *in vitro* colonies if an *in-vivo* equivalent of heterogeneous drug handling due to cellular organization can be shown.

Homozygous deletion of $p16^{MTS-1}$ in gastric cancer cell lines

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$p16^{MTS-1}$ is a tumour suppressor gene that acts by inhibiting cyclin dependent kinase 4. A germ line mutation appears responsible for familial melanoma and the gene is mutated/deleted in a number of cancer cell lines. Its role in gastric cancer is unknown. In this study the gene in gastric cancer cell lines was examined.

DNA was extracted from five gastric cancer cell lines (MKN45, St42, St16, Kato III and AgS). Specific primers were designed for the three exons comprising the entire open reading frame of the p16 gene. The DNA was amplified by polymerase chain reaction, the products being resolved by polyacrylamide gel electrophoresis.

In all cell lines except AgS there was homozygous deletion of the entire p16 coding sequence. Loss of p16 may allow persistence of gastric cancer cells in culture and the role of p16 in gastric tumours warrants investigation.

Fluorescence-based examination of the efficacy of intravesical epirubicin

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Anthracyclines such as epirubicin and doxorubicin are commonly used in cancer chemotherapy. Resistance to these agents is common, and implies the presence of multidrug resistance (MDR). Decreased cellular drug levels characterize MDR. Intravesical use of these agents in the treatment of bladder cancer is well established. Sensitive and resistant MGH-U1 bladder tumour cells were used to investigate the potential for improving therapy by manipulating extracellular pH, varying drug lipophilicity and incorporating a MDR reversing agent into an *in vitro* model.

Sensitive and resistant tumour cells were grown as monolayers. Procedures were performed *in situ* for confocal microscopy; cells were monodispersed in suspension for flow cytometry. Epirubicin dose response and rate of uptake have been established previously. The chosen regimen was 2 h.

Resistant cells take up eight times less drug than sensitive cells by flow cytometry ($P<0\cdot001$). Confocal microscopy demonstrates drug localization to be punctuate and cytoplasmic in resistant cells; nuclear in sensitive cells. Drug accumulation in resistant cells can be increased to sensitive levels using MDR reversor verapamil 100 μg ml^{-1} ($P<0\cdot001$). Increasing extracellular alkalinity from 6·0 to 7·6 also increases epirubicin uptake in sensitive cells as well as resistant cells treated with verapamil ($P<0\cdot001$). Resistant cells show no such effect.

These results suggest that influencing drug handling may considerably increase efficacy in regional delivery systems such as intravesical chemotherapy.

Perivascular innervation and ultrastructure of blood vessels in liver metastases in an animal model

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The authors have previously demonstrated abnormal innervation of blood vessels in human colorectal liver metastases. This information is now being utilized to enhance cytotoxic perfusion of liver metastases. Fibrosarcoma MC28 and adenocarcinoma HT29 were introduced intraportally in the rat, resulting in multiple liver metastases, to determine the optimum dose of drug and pharmacological modulator. Areas of normal liver and liver metastases were studied immunohistochemically for the presence of protein gene product (PGP) 9·5, neuropeptide Y (NPY), tyrosine hydroxylase (TH), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP) and substance P (SP). Perivascular innervation and ultrastructure of blood vessels were also examined by transmission electron microscopy.

In both models perivascular nerve fibres containing PGP, NPY, TH, CGRP and SP were observed around the interlobular blood vessels and in the portal tract within the normal liver. The highest density was seen for PGP. In contrast, no perivascular immunoreactive nerve was seen in either the MC28 or HT29 liver tumours. Similarly, electron microscopy confirmed the absence of perivascular nerves in the HT29 tumour. Smooth muscle cells were not observed in any tumour blood vessel.

These results demonstrate similarity with human colorectal liver metastases and indicate that this model is suitable for pharmacological studies on vascular manipulation of hepatic artery infusion chemotherapy.

Staging breast cancer with magnetic resonance imaging

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Accurate preoperative locoregional staging of breast cancer may contribute both to planning primary treatment and assessing prognosis. While triple assessment achieves high diagnostic accuracy in breast cancer, it has limitations in defining the local extent of disease and axillary node metastases. The potential role of magnetic resonance imaging (MRI) in breast cancer staging compared with that of clinical and mammographic examinations was evaluated. Sixty women with primary breast cancer were prospectively evaluated by MRI and mammography.

MRI was performed using a dedicated received-only double breast coil on a 1 T scanner (Magnetom 42 SP, Siemens, Germany) using a T1-weighted three-dimensional fast low angle shot sequence before and after enhancement with gadolinium.

MRI and mammography were concordant in 36 patients (60 per cent) with 31 unifocal and five multifocal cancers. Of the 24 patients (40 per cent) with discordant results, mammography was normal ($n = 13$), falsely negative for multifocal cancer ($n = 9$) and falsely positive for multifocal cancer ($n = 2$). MRI identified all but three invasive cancers (each 4 mm in size) which were obscured by areas of diffuse patchy enhancement. In three patients, breast MRI showed an additional enhancing focus not confirmed histologically. Tumour size and stage measured by MRI had a significantly better correlation with histopathological analysis than did mammography ($r = 0{\cdot}86$ *versus* $r = 0{\cdot}45$). In addition, MRI had higher sensitivity than mammography for detecting extensive intraduct component (70 per cent *versus* 40 per cent). Mammography was not useful in diagnosing axillary node metastases. MRI was able to assess the axillae in 45 of 60 patients, with a sensitivity and specificity for axillary node metastases of 90 per cent and 95 per cent respectively.

In conclusion, MRI is of value in the preoperative locoregional staging of primary breast cancer.

How useful is magnetic resonance imaging in detecting recurrence in the conserved breast after cancer surgery?

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The detection of local recurrence after conservative surgery and radiotherapy for breast cancer is often a diagnostic dilemma. Magnetic resonance imaging (MRI) with gadolinium enhancement is a new and potentially useful investigation. The findings of 26 MRI examinations performed during follow-up in 21 patients (average age 55·5 (range 39–74) years), who had previously undergone conservative treatment for breast cancer are reported.

The indications for MRI were suspected local recurrence on clinical or radiological grounds without a definitive diagnosis. The examination was carried out with 1·5 T IGE Sigma Advantage System using a fast multiplaner spoiled grass sequence with chemical saturation pre and post 20 ml gadolinium–diethylenetriamine penta-acetate boluses. The mean interval between surgery and MRI was 47 months (range 16 months–10 years). True negative is defined as a combination of a no enhancement on MRI, along with no clinical recurrence during the subsequent 12-months follow-up.

Results of the 26 MRI examinations included eight true positive, 14 true negative, three false positive and one false negative. Sensitivity was 89 per cent and specificity 73 per cent. Furthermore, MRI directly influenced management in 11 patients: MRI led to the surgical excision of an impalpable lesion not seen on mammography in three patients. Negative MRI avoided needless intervention in a further eight patients with highly suspicious mammography.

MRI is a useful tool in the difficult assessment of the breast after surgery and radiotherapy.

Vascular heterogeneity in breast cancer assessed by microangiography and immunohistochemistry

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Tumour vascularity is an important predictor of prognosis in breast cancer and is currently assessed immunohistochemically on histological sections. This method assumes that the microvascular density is homogeneous, but little has been done to confirm this. Breast microangiography was performed to assess whole tumour vascularity and the findings were compared with those found immunohistochemically on sections from different areas of the tumour.

After mastectomy for primary breast cancer, vessels were cannulated using a 2 Ch catheter and a contrast mixture of barium, gelatin and formalin injected. The resulting mammograms were graded 1–3 for vessel density. Sections (4 μm) were taken from either end of the tumours as well as from the centre, and labelled for vascular endothelium using anti-CD34.

Twenty microangiograms have been completed. Tumours radiologically assessed as grade 1 had a mean vessel count of 41, those assessed as grade 2 a mean count of 77 and grade 3 angiograms a mean count of 162 ($P < 0{\cdot}003$, Kruskal–Wallis one-way analysis of variance). Immunohistochemical heterogeneity was present in six of 20 cases, two of which had been predicted by the microangiograms.

Tumour heterogeneity is present, but with concordance of 70 per cent between blocks and significant concordance with tumour angiography. The authors believe that angiogenic potential can be assessed from one tumour section making this practical for routine clinical use.

Breast tumours stimulate angiogenesis through increased release of macrophage-derived vascular endothelial growth factor

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Angiogenesis is essential for the growth and dissemination of tumours. Vascular endothelial growth factor (VEGF), the angiogenic factor, may thus play a role in tumour growth. The source of tumour-derived VEGF and the mechanism of its release have not been fully clarified. In view of the inverse relationship between macrophage content in breast tumours and prognosis, the authors have hypothesized that the macrophage is the source of tumour VEGF and that its release is controlled by the interaction of tumour cells, macrophages and the tumour environment. Serum VEGF was assayed in patients undergoing breast surgery. Blood samples were collected from patients with benign fibroadenoma ($n = 8$) and breast carcinoma ($n = 10$) before operation and the serum assayed for VEGF by capture enzyme-linked immunosorbent assay (ELISA). To simulate the tumour environment, human peripheral blood monocytes were cultured *in vitro* for 72 h, activated with γ-interferon and incubated under hypoxic conditions with breast tumour cell-conditioned media. Culture supernatants were assayed for VEGF by ELISA.

Samples from patients with malignancy had higher levels of VEGF than those from patients with benign disease (mean(s.d.) 6·35(3·79) *versus* 1·64(1·65) pg VEGF per mg serum protein, $P = 0{\cdot}005$, Student's t-test). Monocytes in tumour-conditioned medium under hypoxic conditions also had increased levels of VEGF compared with those in control medium (56·38 (9·53) *versus* 0·1(0·14) pg VEGF per μg monocyte-derived macrophage).

This study demonstrates increased circulating levels of VEGF in patients with malignant breast disease. The results also indicate that breast tumour cells produce a soluble factor which stimulates macrophage production of VEGF under hypoxic conditions, implicating tumour-associated macrophages as the primary producer of this angiogenic factor in breast cancer.

Serum vascular cell adhesion marker is an endothelial cell marker for angiogenesis

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Angiogenesis is a prerequisite for tumour metastasis and growth. E selectin (Esel) and vascular cell adhesion marker (VCAM) are specific endothelial cell (EC) markers, the soluble forms of which have recently been shown to mediate angiogenesis. As tamoxifen hormonal therapy for metastatic breast cancer inhibits angiogenesis, serum levels of these EC markers were assayed alongside von Willebrand factor (vWF), another EC product, in 24 women undergoing hormonal therapy for breast cancer to determine whether these markers could be used to measure tumour angiogenesis.

Tumour response was assessed by Union Internacional Contra la Cancrum criteria and blood obtained for serum markers (by enzyme-linked immunosorbent assay) at day 0 and 3-monthly intervals. Twelve women had a response to treatment while 12 progressed.

	Esel (ng ml^{-1})	vWf (units dl^{-1})	VCAM (ng ml^{-1})
First stable	57 (51–65)	101 (94–121)	517 (286–662)
Second stable	56 (30–65)	91 (94–115)	423 (339–560)
First progression	46 (33–58)	113 (102–143)	533 (416–991)
Second progression	62 (33–107)	134 (120–156)	970 (632–1895)*

Values are median (interquartile range). $^*P = 0{\cdot}005$ (Wilcoxon signed rank test)

Initial levels of Esel, vWf and VCAM did not differ between patients who subsequently responded and those who did not. All markers decreased in responding patients but only VCAM significantly increased in women whose tumour mass progressed.

Antiangiogenic drugs are currently undergoing phase I trials. VCAM is a potential serum marker of angiogenesis that could be used to assess responses to antiangiogenic therapy.

Magnetic resonance mammography in the investigation of suspected tumour recurrence after breast-conserving treatment

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Suspected tumour recurrence in the surgically conserved breast often poses diagnostic difficulties. These may not be resolved by clinical examination, imaging or fine-needle aspiration cytology or core biopsy. Resultant surgery to establish the diagnosis adds further to patient anxiety, may result in breast disfigurement and induces more scar formation. There is a need, therefore, to evaluate new diagnostic modalities. Dynamic gadolinium (Gd)-enhanced magnetic resonance mammography (MRM) has been recently introduced into clinical practice. MRM was used to evaluate 37 consecutive patients who had undergone breast conservation treatment and who had clinical and/or imaging (mammographic) suspicion of recurrent disease. The time from original treatment was 1–10 years.

MRM was performed on a Magnetom Impact 1·0 T (Siemens) using a double breast surface coil. Both breasts were imaged in their entirety in the axial plane once before Gd enhancement and three times after Gd enhancement. Total imaging time was under 20 min. Enhancing lesions were identified using image subtraction software (MammaCalc, Siemens) and sites of maximum enhancement were quantitatively analysed using the indices ΔS_1 and ΔS_{max} ($\Delta S_1 = (S_1 - S_0)/0{\cdot}5(F_0 + F_1)$ and $\Delta S_{max} = (S_{max} - S_0)/0{\cdot}5(F_0 + F_{max})$). Lesion signal change is expressed as a fraction of the mean fat signal, with S_0, S_1 and S_{max} being lesion signal intensity before Gd enhancement, 1 min after Gd enhancement and at maximum enhancement. F_0, F_1 and F_{max} are the respective signals from a region close to the lesion. Eleven patients (11 mammographic, one clinical abnormalities) had enhancing lesions. All lesions with ΔS_1 greater than 0·30 (five of 11 patients) had invasive cancer (confirmed by biopsy). Lesions with ΔS_1 less than 0·30 (six of 11 patients) had benign disease (confirmed by cytology or biopsy). The remaining 26 patients showed no enhancement, diagnosis was confirmed by negative biopsy (three), negative cytology (17) or clinical and imaging follow-up (six).

Quantitative MRM is helpful in discriminating recurrent from post-treatment change in the breast and the index ΔS_1 less than 0·30 was an accurate predictor (100 per cent) of the absence of tumour recurrence in this series.

Histopathological parameters reflect the increased aggressiveness of comedo ductal carcinoma *in situ*

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The incidence of ductal carcinoma *in situ* (DCIS) has increased from less than 5 per cent of all breast carcinomas to more than 25 per cent following the introduction of screening mammography. Treatment with mastectomy produces excellent results, however these patients are now being offered breast conservation. Unfortunately, the natural history of these lesions is unknown, but it appears that comedo DCIS is biologically more aggressive and more likely to progress or recur. Mitotic count, nuclear grade, S-phase fraction, ploidy, microinvasion and p53 staining were examined in a consecutive series of 100 patients with DCIS, to determine whether the greater tendency of comedo DCIS to recur was reflected in histological parameters.

	Comedo	Cribriform	Other
No. of patients	57	29	14
Age (years)	57·5(1·2)	56·8(2·0)	54·5(1·9)
Mitotic count	12·0(0·8)	3·2(0·5)*	5·0(1·0)*
Nuclear grade	2·9(0·1)	1·3(0·1)*	1·9(0·2)*
S-phase fraction	9·8(1·3)	7·8(1·9)	6·5(2·5)
Diploid (%)	26 (46)	17 (59)	7 (50)
p53 positive (%)	16 (28)	1 (3)	2 (14)
Microinvasion (%)	13 (23)	4 (14)	5 (36)

Values are mean(s.e.m.). *$P > 0·05$ (Mann–Whitney U test, χ^2 test)

This study demonstrates that comedo DCIS has a significantly greater mitotic count, nuclear grade and that more patients are p53 positive than those with cribriform DCIS.

In conclusion, histological parameters reflect and may provide a useful measure of the increased biological aggression traditionally associated with comedo DCIS.

Cyst type and breast cancer risk

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A total of 3041 cyst fluids were aspirated from 1374 patients from 1981 to 1989. Cyst fluids were classified as type I $[\mathrm{Na}^+]/[\mathrm{K}^+]$ less than 3 or type II $[\mathrm{Na}^+]/[\mathrm{K}^+]$ equal to or greater than 3. From Cancer Registry data 60 patients had developed breast cancer by the end of 1993. The current analysis relates to cysts aspirated at the initial clinic visit. Patients were classified into three groups; type I cysts only ($n = 451$), type II cysts only ($n = 741$), or mixtures of the two types ($n = 182$).

A Cox proportional hazards regression analysis has been performed relating breast cancer risk to (i) cyst type at initial presentation (types I or II or mixture), (ii) age of the patient at presentation, and (iii) number of cysts aspirated at the first clinic visit. No difference in cancer incidence was evident between any of the three groups of patients classified on the basis of cyst type: in particular, the 95 per cent confidence interval for the hazard ratio for type II *versus* type I cysts was 0·47–1·39. Neither age nor number of cysts aspirated at the initial clinic visit was significantly associated with subsequent cancer incidence.

This preliminary analysis suggests that if there is an excess risk of breast cancer in patients with type I cysts then the magnitude of this risk is less than two.

Colour flow Doppler in assessment of malignant breast disease

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Colour flow Doppler (CFD) is a sensitive modality for detection of disordered blood flow and increased angiogenesis in malignant breast lesions and lymph nodes.

CFD was undertaken in 20 patients (median age 59 (range 40–85) years) with malignant breast disease and the findings compared with those from mammography, cytology (FNAC), and histological assessment of tumour size, grade, type, presence of vascular invasion and lymph node involvement.

Patients were scanned radially from the nipple and in transverse/transductal planes using an ATL Doppler with a 7·5–13 MHz linear array transducer. Scans were graded blind by video analysis to give a CFD index (CFDI) of 0–4 for malignancy, on the basis of enhanced colour flow intensity, abnormal flow patterns and peak systolic velocities. The normal breast was used as a control.

Sensitivity of CFD in detection of malignancy was 100 per cent. In one case, increased flow (CFDI-1) in a patient with previous excision of a medullary carcinoma suggested local recurrence, which was not confirmed by FNAC/mammography. This gave rise to one false-positive result (specificity 50 per cent). Correlation of tumour size determined by CFD with histological evidence ($r = 0·97$) was closer than the correlation derived by mammography ($r = 0·85$). CFD detected three diffuse tumours in which mammography was negative or equivocal. In one 83-year-old patient with infiltrating lobular carcinoma, the CFDI decreased from 3 to 2 following 4 months of treatment with tamoxifen. In a further 49-year-old patient, histologically confirmed involution of a tumour 3 node 0 metastasis 0 tumour following neoadjuvant chemotherapy was reflected by loss of malignant features and return of the CFDI to 0.

CFD is a sensitive modality to complement mammography and FNAC in the detection of breast malignancy. It may also fill a useful role in the assessment of the physiological effects of adjuvant therapy on tumour neovascularization.

Treatment with a human leucocyte antigen peptide and cyclosporin A prolongs survival of small bowel allograft in the rat

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Current immunosuppression for small bowel transplantation (SBT) is relatively ineffective and toxic. Recently, an HLA-B7 peptide fragment (residues 75–84) that blocks cytotoxic T cell precursor differentiation *in vitro* has been identified. In rodents, recipient combination treatment with this peptide and subtherapeutic doses of cyclosporin A (CsA) prolonged cardiac and skin allograft survival, without altering the recipient's rejection kinetics to third-party allografts. This new immunosuppressive approach in SBT was investigated.

Heterotopic allogeneic SBT was performed in the DA (RT1a) to Lewis (RT1l) high responder rat strain combination. HLA-B7 75–84 40 mg kg^{-1} day^{-1} and subtherapeutic CsA 10 mg kg^{-1} day^{-1} were administered alone, or in combination, by gavage to the recipient on days 0 to 4 after SBT. Graft rejection was determined by the presence of a palpable abdominal mass on daily clinical examination or loss of greater than 10 per cent initial body weight.

	Median graft survival (days) (range)
No immunosuppression ($n = 7$)	6 (5–7)
CsA alone ($n = 6$)	6 (6–7)
HLA-B7 75–84 alone ($n = 6$)	5 (5–6)
CsA and HLA-B7 75–84 ($n = 9$)	11 (9–13)*

*$P < 0·001$ *versus* no immunosuppression, CsA alone and HLA-B7 75–84 alone (Mann–Whitney U test)

Treatment with B7 75–84 produced significant improvement in graft survival only after combination with subtherapeutic CsA. This synergistic effect may be valuable in achieving improved SBT survival clinically and warrants further exploration.

Increased release of interleukin 8 from blood mononuclear cells by indomethacin in patients with acute pancreatitis

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Release of interleukin 8 (IL-8) from peripheral blood mononuclear cells (PBMC) is increased in patients with acute pancreatitis on admission compared with that in healthy volunteers. Furthermore, severe disease is associated with a greater duration of increased IL-8 release than mild disease. Products of the cyclo-oxygenase system are recognized to be important in the control of tumour necrosis factor release but the regulatory mechanisms for IL-8 are less well known. The release of IL-8 into the cell culture supernatant of PBMC after 24-h incubation in the presence or absence of indomethacin (10^{-6} mol l^{-1}), a cyclo-oxygenase inhibitor, was measured. Cells were isolated from six healthy volunteers and 14 patients with acute pancreatitis (six severe, eight mild: Atlanta classification) on the first and fifth day of admission.

	IL-8 according to disease severity (ng ml^{-1})		
	Control	Mild	Severe
Admission day 1			
No indomethacin	35·0 (16·5)	146 (45·9)	174 (49·7)
Indomethacin (10^{-6} mol l^{-1})	37·6 (20·0)	246 (53·7)*	277 (71·9)*
Admission day 5			
No indomethacin		50·1 (24·8)	131 (28·7)
Indomethacin (10^{-6} mol l^{-1})		93·9 (44·3)†	233 (57·8)‡

Values are mean (s.e.m.). *$P<0{\cdot}02$ *versus* no indomethacin; †$P<0{\cdot}05$ *versus* no indomethacin; ‡$P<0{\cdot}04$ *versus* no indomethacin (paired t-test)

Indomethacin had no effect on IL-8 release from PBMC in the control group, while it significantly increased IL-8 release in patients with mild and severe disease. By day 5, there was no significant difference in IL-8 release in patients with mild disease compared with that in healthy volunteers ($P=0{\cdot}78$, Mann–Whitney U test) but PBMC from patients with pancreatitis still manifest increased IL-8 release when exposed to indomethacin.

These observations suggest that a product of the cyclo-oxygenase pathway is induced in PBMC to minimize the increased release of IL-8 observed in patients with acute pancreatitis. Such regulatory control is inhibited by indomethacin and the use of such agents may adversely influence proinflammatory cytokine release in patients with acute pancreatitis.

Oxygen-derived free radicals and histamine in gastroduodenal lesions

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Patients with peptic ulcer have lowered mucosal histamine in the stomach and duodenum, which rises to control values after therapy. The role of duodenal histamine is not clear. Recently, it has been suggested that *Helicobacter pylori* lowers oxyntic mucosal histamine; also that severe duodenitis and duodenal ulcer (DU) are associated with massive production of oxygen-derived free radicals (ODFR) which has been implicated in the mechanism of DU relapse. In the small intestine xanthine oxidase (XO) generates ODFR and may be activated by xanthine dehydrogenase (XD) conversion or histamine in ischaemia. The aims of the present study were to investigate the effect of *H. pylori* infection on histamine concentration in patients with gastroduodenal lesions, and the possible mediation of the production of ODFR in duodenum.

Symptomatic patients were classified at endoscopy into three groups: those with no visible lesions (N; $n=27$); those with duodenitis or DU (DL; $n=18$); and those with gastritis or gastric ulcer (GL; $n=20$). Biopsy specimens were taken from the corpus, antrum and duodenum. Antral biopsy specimens were tested for *H. pylori* by urease test and culture. Gastric biopsy specimens were assayed for histamine concentration and histamine methyltransferase (HMT) activity, and duodenal biopsy specimens for histamine concentration, and xanthine dehydrogenase and XO activity.

In the GL group, *H. pylori* was associated with lowered oxyntic ($P=0{\cdot}002$, Mann–Whitney U test) and duodenal mucosal histamine ($P=0{\cdot}02$). Group DL had lower mucosal oxyntic ($P=0{\cdot}002$) and duodenal histamine ($P<0{\cdot}05$) irrespective of *H. pylori* infection. Similarly, group GL had lower oxyntic histamine irrespective of *H. pylori* ($P=0{\cdot}002$). Duodenal lesions were associated with high XO but lower XD activities. Gastric lesions had no effect on duodenal XO but lowered XD. Duodenal mucosal histamine and XD were inversely related in group N ($R_S=0{\cdot}66$, $P=0{\cdot}02$, Spearman's rank correlation coefficient).

It is concluded that ODFR may be inflicting injury by releasing histamine from its storage which acts as a local inflammatory agent.

Oesophageal bile reflux increases following cholecystectomy

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Increased gastro-oesophageal acid reflux has been shown to contribute to postcholecystectomy symptoms but gastro-oesophageal bile reflux has not been studied. Oesophageal bile reflux has previously been inferred from alkaline pH shift but more recently a fibreoptic probe has become available allowing direct ambulatory measurement.

Twenty patients have been entered into an ongoing prospective study, undergoing 24-h ambulatory oesophageal pH and bile monitoring plus manometry before and 3 months after cholecystectomy. Nine patients have returned for postoperative studies to date.

	Preop.	Postop.
Bile reflux median (range) (per cent time absorbance greater than 0·14)	1·0 (0·1–1·7)	11·1 (0·3–32·0)*
DeMeester score mean (s.e.m.)	12·3 (1·7)	22·6 (6·5)*
LOSP (mmHg) median (range)	10 (8–10)	10 (10–12)

*$P<0{\cdot}05$ (Wilcoxon signed rank test). LOSP, Lower oesophageal sphincter pressure

Gastro-oesophageal bile and acid reflux increased following cholecystectomy. This occurred without any change in lower oesophageal sphincter pressure. There was also no correlation between bile reflux and per cent time oesophageal pH greater than 7·0 ($r=0{\cdot}05$, $P=0{\cdot}61$, Pearson's correlation coefficient).

Alkaline pH shift in the oesophagus is a poor marker for bile reflux. Increased bile and acid reflux into the oesophagus may contribute to the postcholecystectomy syndrome.

Hepatic macrophage blockade improves survival and diminishes plasma tumour necrosis factor following intraperitoneal endotoxin in experimental obstructive jaundice

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Invasive procedures are frequently complicated by Gram-negative sepsis and endotoxaemia in patients with obstructive jaundice. Hepatic macrophages (HΦ) are the major producers of proinflammatory mediators such as tumour necrosis factor (TNF). Increased secretion of TNF by HΦ after exposure to endotoxin may contribute to the pathophysiology of septic complications in obstructive jaundice. The role of HΦ in response to exogenous endotoxin (LPS) in experimental obstructive jaundice using gadolinium chloride (GdCl) to block HΦ function was investigated.

Forty male Wistar rats (275–325 g) underwent bile duct ligation (BDL). On day 19 animals were randomized to receive an intravenous solution of GdCl 10 mg kg^{-1} (BDL-GdC1) or saline (BDL-saline). Animals were studied on day 21. Two experiments were performed: 10 animals from each group were challenged with intraperitoneal (IP) LPS (*Escherichia coli* B4 0111) 0·02 mg per 100 g. Survival was assessed after 4 h (experiment 1). The remaining 10 animals in each group were challenged with IP LPS 0·0002 mg per 100 g and killed after 1 h (experiment 2). Plasma TNF was assayed by enzyme-linked immunosorbent assay. Data are expressed as median (interquartile range).

	BDL-saline	BDL-GdCl
Survival in experiment 1 (%)	50	100*
TNF in experiment 2 (pg ml^{-1})	15335 (436–27873)	88 (0–1319)†

*$P<0·001$, Yates corrected χ^2 test = 10·8; †$P=0·03$, Mann–Whitney *U* test

Blockade of HΦ improved survival after high-dose LPS and suppressed TNF secretion after low-dose LPS. Hypersecretion of TNF by HΦ may be a feature of the response to LPS in experimental obstructive jaundice. These data suggest that hypersecretion of TNF by activated HΦ may mediate septic complications in experimental obstructive jaundice.

Endoscopic injection for bleeding peptic ulcer: a comparison of adrenaline alone with adrenaline plus human thrombin

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Endoscopic injection therapy with diluted adrenaline improves outcome in bleeding peptic ulcer, but 15–24 per cent of patients rebleed despite optimum injection. Human thrombin may more effectively thrombose the bleeding artery, but is associated with the risk of local and systemic complications.

A total of 105 patients with significant peptic ulcer haemorrhage and endoscopic stigmata of recent haemorrhage were randomized to endoscopic injection with 4–18 ml 1 : 100 000 adrenaline (52 patients; group 1) or adrenaline plus 600–1000 units human thrombin dissolved in 40 mmol l^{-1} calcium chloride (53 patients; group 2). The two groups were well matched for age, shock, haemoglobin concentration, endoscopic findings and consumption of non-steroidal anti-inflammatory drugs.

No complications of therapy occurred. Eleven patients (21 per cent) in group 1 and three (6 per cent) in group 2 rebled ($P<0·05$). Mortality, transfusion requirements and hospital stay were similar in the two groups.

Human thrombin injection appears to be safe and may represent the best treatment for bleeding peptic ulcer.

Amelioration of acute pancreatitis using a tumour necrosis factor–metalloproteinase inhibitor

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Tumour necrosis factor (TNF) is a potent proinflammatory cytokine that has been shown to be an important mediator in the development of both local and systemic sequelae associated with severe acute pancreatitis.

The effect of a TNF–metalloproteinase inhibitor, BB1101, known to be active at the post-translational step in TNF production, was studied in the microvascular ischaemic model of acute pancreatitis in male Wistar rats. Administration of BB1101 (3 mg kg^{-1}), given as a single intraperitoneal dose 30 min *after* induction of acute pancreatitis, significantly reduced ($P=0·01$) the rise in serum amylase (mean 2083 (range 1646–2843) in treated animals *versus* mean 2623 (range 2071–3058) in controls), pancreatic weight ($P<0·005$) (mean 1·16 (range 0·84–1·4) g in treated animals *versus* mean 1·75 (range 0·96–2·23) g in controls) and histology score ($P<0·001$) (mean 8·25 (range 5–11) in treated animals *versus* mean 17 (range 14–20) control pancreata).

Pancreatic tissue levels of TNF are increased in experimental acute pancreatitis. Treatment with a TNF–metalloproteinase inhibitor can ameliorate disease progression and this may represent a new therapeutic strategy.

Multiple organ failure in acute pancreatitis is ameliorated by treatment with Lexipafant

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The mortality rate from acute pancreatitis is still 9–11 per cent. Clinical trials targeting the pathophysiology of the disease have failed to show any significant improvement in clinical outcome. A randomized, double-blind placebo-controlled trial of a platelet-activating factor receptor antagonist, Lexipafant, in the treatment of severe acute pancreatitis was conducted. Inclusion criteria were: (i) admission within 72 h of the onset of pain; (ii) serum amylase greater than four times the upper limit of normal; and (iii) (a) APACHE II score greater than 5 or (b) greater than or equal to 3 Glasgow prognostic score or (c) C-reactive protein 120 mg l^{-1} or more. The study had full ethical approval from participating hospitals. Some 188 patients with acute pancreatitis were screened and 51 recruited: Lexipafant ($n=27$) and placebo ($n=24$). Patients received a continuous intravenous (iv) infusion of placebo or 100 mg Lexipafant day^{-1} for 120 h (APACHE 6–8), for 168 h (APACHE greater than 8) or until iv hydration was discontinued. Patients were clinically assessed daily for 8 days and organ failure (OF) scores calculated. The results are summarized below.

	Lexipafant ($n=27$)	Placebo ($n=24$)
OF on admission	16	9
OF at 7 days	7	8
Mortality (all causes at 90 days)	4	6
Mean(s.d.) change in OF score from baseline	− 1·33(1·44)*	0·17(1·97)

*$P=0·005$ *versus* placebo, Wilcoxon rank sum test

These results strongly suggest that Lexipafant ameliorates multiple OF in severe acute pancreatitis.

Positron emission tomography using fluorodeoxyglucose for imaging pancreatic carcinoma

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A range of conventional imaging techniques have been used to examine the pancreas in various pathophysiological disorders.

However, these modalities have varying sensitivities and often lack sufficient specificity to provide definitive diagnosis. In contrast, positron emission tomography (PET) provides an *in vivo* insight into normal and diseased tissue function. Positron emitter-labelled metabolic substrates are introduced into the circulation; following tissue uptake, and subsequent decay, photons are released, detected by coil magnets and registered accordingly. Fluorodeoxyglucose (FDG) is a positron emitter-labelled glucose analogue that demonstrates preferential uptake by human tumours, compared with that in normal tissue. This increased uptake is secondary to increased glycolysis and enhanced membrane transport. Pancreatic adenocarcinoma has also been shown to have increased expression of the glucose transporter GLUT-1 gene. The aims of this study, therefore, were to evaluate the role of FDG PET in imaging pancreatic carcinoma and to assess the feasibility of superimposing the metabolic information obtained by PET with the anatomical details from magnetic resonance imaging (MRI).

Eight patients with proven pancreatic carcinoma were studied. MRI images were obtained before PET imaging. After intravenous injection of FDG, axial PET images were obtained using the ECAT II scanner in five planes straddling the tumour location as identified by MRI. The images were reconstructed and superimposed on the MRI images. Tumours were successfully imaged in all cases. Combined images permitted the visualization of tumour topography and metabolic activity. These qualitative data may permit more accurate differentiation between neoplastic and inflammatory activity. Repeated quantitative analysis of metabolic activity may provide a basis for detailed evaluation of treatment effects.

British Journal of Surgery 1996, 83, 708–715

Correspondence

Randomized trial of laparoscopic cholecystectomy and mini-cholecystectomy

Sir

We read with interest the article by Mr McGinn and co-workers (*Br J Surg* 1995; 82: 1374–7) comparing the advantages and disadvantages of laparoscopic cholecystectomy and mini-cholecystectomy. We are pleased that a number of surgeons around the world agree that there are other minimally invasive alternatives to laparoscopic cholecystectomy, some of which may be superior.

In the study by Mr McGinn and colleagues laparoscopic cholecystectomy had a higher conversion rate than mini-cholecystectomy (13 *versus* 4 per cent) and a higher rate of postoperative complications (10 *versus* 3 per cent). Although allowance must be made for the temporary learning curve of young surgeons, one may question whether the increased surgical time and the higher conversion and complication rates are compensated by 1 day less of hospitalization, less pain medication and a shorter recuperation time. In elderly patients and especially those with chronic cardiopulmonary disease, the CO_2 insufflation of the abdomen provides an extra risk factor.

Between December 1990 and October 1995, 1116 microlaparotomy cholecystectomies have been performed in unselected patients in our department. All microlaparotomy procedures have been performed by one surgeon (S. Rozsos), while the other staff surgeons have performed laparoscopic cholecystectomy. In 94 per cent of patients a vertical midline abdominal incision was used, passing upwards from the base of the subxiphoid (infrasternal) triangle. The upper tip of this triangle is at the xiphoid process and the base is between the left and right angles of the 9th ribs. Abdominal pressure changes are more prevalent in the area above the umbilicus, which is why incisional hernias are more frequently seen with upper midline laparotomies[1]. A long incision in this area is more painful than a short 4-cm one starting from the base of the triangle, as this area is less involved in respiratory muscle movements. The microlaparotomy incision lies above Calot's triangle, which comes closer to the abdominal skin when the patient is placed in the correct position required for this procedure. Using specially developed retractors with large fibreoptic cables and a high intensity illuminator, one can achieve excellent exposure of the biliary system with superb illumination[2].

In our department we have been performing laparoscopic cholecystectomy since 1992 for relatively uncomplicated cases. In a non-randomized retrospective study, we compared 280 patients who had recently undergone laparoscopic cholecystectomy with 280 of those who had recently had mini-cholecystectomy. There were no deaths in either group. Some 16 patients (5·7 per cent) in the group who had laparoscopic cholecystectomy required conversion but none in the group who had undergone mini-cholecystectomy. Postoperative complications occurred in 13 patients (4·6 per cent) of the laparoscopic cholecystectomy group and one (0·4 per cent) in the mini-cholecystectomy group. Early reoperation was required in four patients (1·4 per cent) in the laparoscopic cholecystectomy group and one (0·4 per cent) in the mini-cholecystectomy group. Mean duration of operation in the laparoscopic cholecystectomy group was 65 min as opposed to 18 min in the mini-cholecystectomy group. We placed both sets of patients in the same room to compare postoperative pain, the need for analgesics, and postoperative mobility. We also compared mean time to return to work. As there were no differences between the two groups, we conclude that mini-cholecystectomy is a safer, more rapid and economically advantageous procedure.

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1 Bugyi I. Repetitorium chirurgiae. *Csongr M Eü Osat* 1970: 210.
2 Rozsos S, Jako G. Microlaparotomy cholecystectomy. *Ann Surg* 1995; 222: 762–3 (Letter).

Cystic duct laceration by metallic clips: a cautionary note

Sir

I was interested to read the case report by Mr Kennedy and colleagues (*Br J Surg* 1995; 82: 1543) in which a cystic duct leaked following the application of a clip during laparoscopic cholecystectomy. May I suggest that diathermy itself can very easily produce similar damage. When a metal clip has been applied to the cystic duct, unless care is taken, a diathermy instrument may brush against this clip, especially if the insulation of the instrument is damaged or deficient. This 'cutting' electric charge arcing down a narrow clip can easily cut into the narrow cystic duct which may then leak. I believe this is a definite risk which should be emphasized and avoided.

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Face masks

Sir

One can see surgeons on the television repeatedly operating with their face mask beneath their nose. I have in mind especially an international surgeon grafting a kidney into an open abdomen fairly recently. This patient no doubt was in an immunologically impaired state. Is it not still the custom to cover both mouth and nose with a mask, or has the old standard of antisepsis now been discarded? In view of the frequency with which one sees this on the television, perhaps interested readers would like to comment with their own views on this practice.

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Long-term follow-up of a prospective randomized study of endoscopic *versus* surgical treatment of bile duct calculi in patients with gallbladder *in situ*

Sir

We read with interest the article by Dr Hammarström and colleagues (*Br J Surg* 1995; 82: 1516–21) but there are a few points to be clarified.

(1) The authors have not stated whether all or some of the patients had cholelithiasis. If these patients did have cholelithiasis, had they been subjected to cholecystectomy? This would have led to fewer biliary complications and episodes of pancreatitis and 'might have cured' one of the patients who died from gallbladder carcinoma (had the growth been intramucosal).

(2) It is not clear why the six asymptomatic patients in the group undergoing endoscopic sphincterotomy were subjected to cholecystectomy.

(3) The authors' suggestion that operation prevented heart-related mortality (presumably myocardial infarction) because of subclinical biliary infection is highly speculative. The hypothesis would suggest that biliary surgery could prevent myocardial infarction. Their second suggestion that 'the diagnosis of cholangitis or cholecystitis was missed, and death erroneously attributed to a cardiac cause' appears more logical. It is also probable that patients undergoing operation were screened and followed more carefully for heart disease than those undergoing endoscopic sphincterotomy.

(4) The median hospital stay of 13 days in the group undergoing endoscopic sphincterotomy appears to be high.

(5) The authors have included complications such as post-operative gastric retention secondary to duodenal ulcer and accidental injury to the duodenum at elective cholecystectomy in the endoscopic sphincterotomy group. These complications are unrelated to endoscopic sphincterotomy and may occur in any patient.

(6) In *Patients and methods*, it was stated that patients' death certificates and/or post-mortem examination reports were reviewed. Were post-mortem reports available in the 16 patients who died from non-biliary diseases? Had they been available, there would not have been any speculation as to the cause of death in those presumed to have heart disease. The authors set up a trial to study the two treatment modalities of managing patients with common bile duct stones, but they actually enumerated the advantages of cholecystectomy.

One aspect of the study appears clear: patients with gallbladder *in situ* and choledocholithiasis may either be managed surgically or, if endoscopic sphincterotomy is performed and the common bile duct is cleared of calculi, then these patients should undergo cholecystectomy as early as possible. Such an approach will prevent biliary complications, acute pancreatitis, the occasional case of gallbladder cancer and, if the authors' contention about heart disease is correct, myocardial infarction also.

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Author's reply

Sir

I should like to reply to the comments of Drs Misra and Dwivedi.

(1) All but two patients in each group had gallbladder calculi. Several studies including one from our department show that as many as 10–20 per cent of patients require cholecystectomy and 2–3 per cent of patients develop gallbladder carcinoma during long-term follow-up after endoscopic treatment of common bile duct stones in patients with gallbladder *in situ*. Whether these figures should justify subsequent routine cholecystectomy or not after endoscopic sphincterotomy is debatable.

(2) The patients and their physicians subsequently, and for various reasons other than biliary symptoms, preferred cholecystectomy to expectant management.

(3) and (6) We did not suggest that there might be an association between biliary disease and myocardial infarction *per se*, but between biliary disease and heart failure, the cause of which may be other than myocardial infarction. For example, a septic condition of biliary origin was erroneously interpreted as death from heart disease, because the biliary origin was not recognized. In this sense, post-mortem examinations in all dead patients would undoubtedly have been valuable, and minimized speculation.

Once the exclusion criteria had been scrutinized and the patients found eligible to enter the study (only six patients were considered unfit for operation; see *Fig. 1* in article), the patients were randomly allocated to endoscopic sphincterotomy or surgery. At this stage there was, of course, no selection.

Both patient groups enjoyed the same care during follow-up. Rightly, the objective of the study was to compare long-term outcome of the two treatment strategies, and the results urged us to conclude that the outcome was similar, but the more frequent non-biliary related deaths in the endoscopic sphincterotomy group might indicate in favour of surgical management.

(4) I am afraid there has been a misunderstanding with regard to the figure of 13 days, which refers to the total length of hospital stay including subsequent periods of hospitalization due to biliary complications in the endoscopic sphincterotomy group. The initial hospital stay, when endoscopic sphincterotomy was performed, was a median of 6 days.

(5) The objective of this study was to investigate total accumulated morbidity during long-term follow-up for patients in the endoscopic sphincterotomy and operation groups. The two noted complications occurred during subsequent necessary intervention after endoscopic sphincterotomy and were thus indirectly caused by this treatment strategy. They represent a long-term drawback of this method, despite the fact that they might have occurred in the patients who underwent surgical treatment as well.

The point mentioned in the last paragraph, namely whether operation in patients with common bile duct stones and an intact gallbladder should be preceded by endoscopic bile duct clearance or not, has been investigated previously (*Table 1* in the article) and was not the objective of this study.

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Mesenteric ischaemia: a multidisciplinary approach

Sir

'Intestinal ischaemia' is a better term than 'mesenteric ischaemia', as it describes the tissue that is ischaemic rather than the artery that supplies it – we do not refer to 'carotid' or 'aortic' ischaemia. The comprehensive review of the recent literature on the subject by Mr Bradbury and colleagues (*Br J Surg* 1995; 82: 1446–59) is a useful contribution. The list of 224 references is quite the longest to appear in the Journal for many years, and indeed is almost as long as the article itself. But by confining themselves to work which has appeared since 1990 they have wandered into a number of fundamental errors and misconceptions. For example, it must be made plain that: (1) ischaemic bowel almost never results in bacteraemia; (2) ischaemic colitis does not lead to toxic megacolon and perforation; (3) chronic ischaemia does not cause malabsorption and does not cause anything like Crohn's disease, unless there is an infarction; and (4) a blocked coeliac axis does not cause gastric and gallbladder dysfunction.

Two areas require more detailed comment. The first concerns the place of aortography in suspected acute ischaemia. The authors suggest that this should be carried out where ischaemic bowel cannot be excluded. But they indicate that the symptoms and signs are non-specific and that there is no reliable laboratory test for the condition, so in theory it can never be excluded, and the absurd position is reached whereby every patient with abdominal pain but no overt peritonitis should have an aortogram. Clearly, what is needed is a prospective trial whereby a defined group of patients with acute abdominal pain who could reasonably be expected to be at risk (the entry criteria might be over 60 years of age, cardiovascular history, taking digitalis, severe colic but no physical signs) is subjected to aortography, and the benefits and drawbacks are assessed. This study would at least provide a measure of the sensitivity of the test: very few proponents of aortography have reported the number of negative examinations, which seems to lie around 50 per cent. The difficulties of organizing such a trial are obviously great and its usefulness is uncertain, which is why most surgeons have continued to treat patients on clinical suspicion, awaiting the time when a reliable laboratory test for treatable (as opposed to fatally infarcted) ischaemic bowel becomes available. Until that time, algorithms such as this, which are great fun to construct, will remain of theoretical interest only.

Second, it is a pity that the authors missed the opportunity to review the one area of the splanchnic circulation in which major advances have been made and treatment influenced. It springs from the realization that the intestinal mucosal or blood barrier is easily breached in all manner of critical situations that can initiate multiple organ failure. Mucosal blood flow can now be accurately and non-invasively measured during operation and in the critically ill or injured patient, and appropriate measures taken. This is the most exciting area in the field and deserves an up-to-date review.

It is wonderful what CD-ROM (compact disk–read-only memory) and a small computer can do these days, but they must be supplemented by use of the critical faculty. Space in an international peer-reviewed journal is precious, and if the authors had pruned out the references with a high 'so what?' index, such as those telling us that tumour embolus of the superior mesenteric artery has been reported following pneumonectomy, or the one about the effects of 21-aminosteroid U-74389G on the ascending colon of the horse, they would have been able to include others from the world literature before 1990 that were more germane to the subject, and of more use to the practising surgeon of today.

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Authors' reply

Sir

We thank Mr Marston for his interest in our recent article and are pleased that he found it to be a 'comprehensive' and 'useful' contribution to what is a large and controversial topic. While we have the greatest respect for Mr Marston's contribution to this field, we refute totally his assertion that we have 'wandered into a number of fundamental errors and misconceptions'. Although constraints on space prevent us from entering into a full discussion of all his points, we wish to respond to his specific criticisms.

(1) Mr Marston may favour the term 'intestinal ischaemia', but perusal of the literature demonstrates that the vast majority of authors choose to use the term 'mesenteric ischaemia'. The latter would, therefore, seem to be the most appropriate for a review.

(2) With regard to bacteraemia, there is an extensive literature demonstrating that mesenteric ischaemia and infarction are accompanied by increases in bowel permeability, bacterial invasion and translocation. Bacteria and their products, such as endotoxin, are widely recognized as contributing to multiple organ failure and death in these patients. Indeed, in a 1992 article, Mr Marston himself made the following comments: 'bacterial invasion and toxaemia clearly demand the use of antibiotics', and 'ischaemia..... allows resident bacteria to become lethally invasive'[1].

(3) Athough uncommon, ischaemic colitis leading to toxic dilatation and perforation is well reported in the literature. For example, in a recent review, Mitsudo and Brandt[2] state that 'toxic megacolon is an uncommon complication of colonic ischaemia but cannot be differentiated from the toxic megacolon seen in other diseases'.

(4) Malabsorption is also reported in association with chronic mesenteric ischaemia by a number of authors. For example, in a recent chapter, Baxter and Pearce[3] included and referenced the following statement: 'there are well documented cases of malabsorption in association with chronic ischaemia; and experimental mesenteric ischaemia results in morphological changes in gut mucosa which would be expected to adversely affect absorption'.

Mesenteric ischaemia may mimic Crohn's disease at both a clinical, operative and histopathological level. There are many references to this fact in papers, review articles, and book chapters[4]. Furthermore, the association does not depend on the presence of acute infarction. For example, Johanns *et al.*[5] described a patient with chronic mesenteric ischaemia who had been wrongly diagnosed as having Crohn's disease for 6 years before successful treatment with aortomesenteric bypass.

(6) Gastric and gallbladder dysfunction is recognized by a number of authors as being responsible for symptoms in a subset of patients with ischaemic bowel; the symptoms may resolve following revascularization[6–8]. What evidence does Mr Marston have that these authors are incorrect in their observations?

(7) The role of angiography in acute ischaemia is certainly a difficult issue and, as such, the advantages and disadvantages are discussed at some length in our review. What is certain, however, is that a more liberal use of angiography is recognized by many leading authorities in the field as a major contributor to the increasingly successful management of these patients. While we agree with Mr Marston that a randomized controlled trial such as the one he proposes would be desirable, we doubt whether it is practicable at the present time.

In summary, with regard to style and content, we find it strange that Mr Marston criticizes us first for omitting references from before 1990, then for an over-extensive bibliography, and then for failing to include a very large additional field such as non-invasive monitoring of mucosal blood flow in critically ill patients. With regard to points of fact, we are confident that we have represented accurately the broad range of opinion to be found in the recent literature.

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Presentation of endometriosis to general surgeons: a 10-year experience

Sir

We read with interest the paper by Mr Singh and colleagues describing experience with endometriosis (*Br J Surg* 1995; 82: 1349–51). We were particularly interested in the section of the paper that dealt with colorectal endometriosis. Authoritative textbooks on colorectal disease describe rectal bleeding, whether cyclical or non-cyclical, as a rare feature of colorectal endometriosis[1]. Our recent experience with four patients with colorectal endometriosis agrees with that of Mr Singh and colleagues in that each patient had some form of rectal bleeding. It seems that rectal bleeding is a much commoner symptom than recognized until now, and its occurrence at or just before the onset of menstruation is pathognomonic of colorectal endometriosis.

We would like to enquire about their findings at colonoscopy. Rowland and Langman[2] reported eleven patients with large bowel endometriosis and could find little evidence of any mucosal abnormality at sigmoidoscopy, despite the presence of a variety of mucosal histological abnormalities ranging from a colitic picture to neoplasia. As a rule, the lesion in the bowel wall is confined to the serosal aspect, the muscularis or the submucosa, with the mucosa remaining intact[3]. We performed colonoscopy routinely in our patients at the time of bleeding but were not able to demonstrate any mucosal abnormality except for a slight increase in vascularity. Biopsies taken from these areas of increased vascularity were reported as histologically normal. In our resected specimens, the lesion was histologically localized to the muscle layer without mucosal involvement. We suggest that the value of colonoscopy lies in the exclusion of other diseases such as colorectal cancer rather than in confirming endometriosis, the presence of which can usually be detected at laparoscopy.

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Authors' reply

Sir

We thank Mr Delicata and colleagues for their comments regarding the use of colonoscopy to diagnose colorectal endometriosis, and empathize with their difficulties in determining mucosal abnormalities in such patients presenting with rectal bleeding. As we have clearly stated in the paper, the first patient had had three rigid sigmoidoscopies and two colonoscopies without identifying a mucosal lesion responsible for bleeding. In the second patient, a greyish, raised, non-ulcerated mucosal abnormality approximately 1 cm in diameter was identified at 28 cm, and biopsied during a colonoscopy carried out at another Edinburgh hospital. At histological examination the biopsy proved to be endometrial tissue. However, in this patient operation was undertaken 18 months later for sigmoid stricturing rather than rectal bleeding. Colonoscopy is only one facet of the investigative process used to reach a diagnosis of endometriosis. The clinical presentation and presence of pelvic endometriosis should alert the clinician to consider endometriosis in the long list of differential diagnosis of lesions causing rectal bleeding. We agree that colonoscopy is the investigation of choice in diagnosing colorectal mucosal lesions that may be responsible for rectal bleeding.

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Factitious disorders and the surgeon

Sir

We read with interest the leading article by Dr Masterton (*Br J Surg* 1995; 82: 1588–9). Patients with factitious disorder, although thankfully rare in general surgical practice, create diagnostic and therapeutic difficulties out of all proportion to their number. A recent report of our own experience revealed nine patients with a diagnosis of factitious disorder among 1644 new referrals with chronic wounds over a 2·5-year period[1]. This represents an incidence of factitious behaviour as the main aetiological factor in non-healing wounds of approximately 0·5 per cent within our clinic. This figure is surprisingly similar to the incidence of factitious disorder of 0·8 per cent seen in patients from a psychiatric consultation service[2]. Both these figures come from tertiary referral centres and may not, therefore, reflect the true incidence of the condition.

Although the self-limiting nature of the disease is discussed, the author gives little practical advice regarding management of these patients and fails to indicate that the most important role of the surgeon is to protect the patient from overinvestigation while resisting surgical attempts to cure the condition. In our series, five patients underwent a total of 36 (range 0–15) operations, of which 60 per cent were performed after the diagnosis of factitious disorder had been suspected. None of the surgical procedures led to prolonged wound healing or resolution of the condition. This fact should not be surprising given that the underlying pathology of the condition is psychiatric and not physical. Surgical intervention should be reserved for limb- or life-threatening complications of this disorder. Early diagnosis remains essential if the patient is not to be exposed to the risk of unnecessary morbidity, and resources are not to be wasted.

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Author's reply

Sir

Thank you for giving me the opportunity to respond to the letter from Drs Baragwanath and Harding. I agree with their principle of *primum non nocere*. I had anticipated that a surgeon would be more circumspect when considering investigations or treatment in a patient who has, or is suspected to have, a factitious disorder – but it is a point worth emphasizing.

A common problem with factitious presentation is uncertainty about the nature of the disorder. Drs Baragwanath and Harding do not seem to encounter this dubiety in their population of chronic wound patients. Nevertheless their prevalence of 0·5 per cent and their conviction that factitious disorders are rare in general surgical practice ought to be qualified as 'recognized' cases.

It is unhelpful to demarcate the surgeon's contribution to a few technical issues. Success requires collaboration among the physical specialists, psychiatrist and general practitioner – a team that may expand to involve the paediatrician and the occupational health physician in the event of proxy disorders being suspected.

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Wandering spleen: a rare emergency condition

Sir

The paper by Dr Papakyriacou and colleagues (*Br J Surg* 1996; 83: 50) on a rare case of wandering spleen brings to mind that this pathology was found, and correctly diagnosed before operation, in one of the first elective splenectomies. The first documented successful splenectomy for a pathologically enlarged spleen was carried out by Jean Péan of Paris in 1867[1]. The patient was a 20-year-old girl with a massive splenic cyst. In March 1892, Sir John Bland-Sutton[2] operated on a girl of 22 years with a painful mobile abdominal mass at Middlesex Hospital, London. His diagnosis before operation lay between wandering spleen and hydatid cyst of the omentum. He replaced the cyst in the left upper quadrant of the abdomen. Recurrence of severe pain forced him to reoperate in July 1892 and remove the spleen, which lay in the pelvis; the pedicle was twisted through three revolutions. The patient recovered uneventfully and was discharged on the 25th day.

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Intermittent vascular exclusion of the liver (without vena cava clamping) during major hepatectomy

Sir

Dr Elias and co-workers (*Br J Surg* 1995; 82: 1535–9) reported their experience with intermittent vascular exclusion of the liver (IVEL) and recommended the use of this new method of vascular isolation of the liver during difficult liver resection, because it avoided vena cava clamping and increased the length of time available for hepatectomy. At our institution, we commonly use vascular exclusion (partial and total) without vena cava clamping for difficult liver resections. We mobilize the whole of the liver in order to gain access to the common trunk of the middle and left hepatic veins, the right and the inferior right hepatic vein. By means of a right-angle dissector, it is possible to isolate the extrahepatic portion of hepatic veins, before its insertion into the suprahepatic vena cava, to allow clamping with vascular clamps. This manoeuvre allows full control of the hepatic veins during resection, and we find it unnecessary to loop the hepatic veins.

In 1995, we performed 18 liver resections with vascular exclusion for hepatocellular carcinoma that were large (more than 10 cm) or situated in difficult anatomical areas. Mean vascular exclusion time was 24·1 min, and mean intraoperative blood loss was 2·3 l (*Table 1*).

Hepatectomy	Cirrhotic	Non-cirrhotic	Duration of clamping (min)*	Mean blood loss (ml)
Right lobe ($n = 12$)	11	1	22·3 (10–35)	2053
Left lobe ($n = 3$)	2	1	27·0 (25–31)	3233
Trisegmentectomy ($n = 3$)	2	1	28·7 (25–34)	2260

*Values are mean (range)

We do not routinely adopt the technique of intermittent declamping and reclamping during liver resection; in our experience, a period of continuous clamping lasting up to 35 min is generally well tolerated in cirrhotic and non-cirrhotic livers.

We agree with Elias and colleagues that vascular exclusion without vena cava cross-clamping is feasible and effective in reducing bleeding. In addition, this technique provides a relatively bloodless operating field and thus allows the procedure to be completed without undue haste. We have found this technique to be adequate and safe for the performance of otherwise difficult and taxing hepatectomies without resorting to clamping the vena cava.

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Laparoscopic hernia repair without the use of staples or knotting manoeuvres

Sir

Various methods of tissue approximation during laparoscopic surgery have been devised in an attempt to avoid the expense of stapling guns or the difficulties associated with laparoscopic suture. The invention of the 'megaknot' by Mr Dunn (*Br J Surg* 1995; 82: 1692) provides an ingenious alternative. We were, however, somewhat concerned at the use of a single ligaclip to secure the other end of the 2/0 polyglactin suture, as *in vitro* studies have shown that neither single, nor double, crossed nor looped ligaclips provide adequate fixation of 2/0 polyglactin suture[1], and they are not designed to do so (personal communication, Ethicon, Edinburgh, UK).

Mesh migration following laparoscopic hernia repair has been implicated in the aetiology of recurrence[2], and this may be attributed to the use of too small a mesh, or inadequate mesh fixation[3,4], particularly at the medial end. The low recurrence rate in the series described (one recurrence in 53 patients), despite what appears to be inadequate mesh fixation, may be attributable to the large size of the mesh, and it calls into question whether the mesh needs to be secured at all.

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Author's reply

Sir

This letter raises some useful points, and I am fully aware of the literature they quote. Based on my experience of 500 laparoscopic hernia repairs, I would comment as follows:

(1) Neither the suture fixing the mesh nor that closing the peritoneum is under any tension at all, and this is probably why the ligaclip has proved to be adequate fixation. It would not be adequate if there were any tension.

(2) My experience leads me to believe that the most important factor in producing the rare recurrences after laparoscopic repair are either too small a mesh, or inadequate preparation of the retroperitoneal 'pouch' so that the mesh curls over when the peritoneal edges are reopposed. Recently, we have stopped fixing the mesh at all, and in an experience of over 75 patients in the past year we have not had cause to regret this omission. The mesh must, however, lie quite 'flat' even when the peritoneum is lifted up over the top of it for closure.

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Preoperative total parenteral nutrition is not associated with mucosal atrophy or bacterial translocation in humans

Sir

We read with interest the paper from Mr Sedman and colleagues (*Br J Surg* 1995; 82: 1663–7) describing their study of intestinal structure and barrier function in patients requiring total parenteral nutrition (TPN) before operation. In patients receiving their nutrition entirely parenterally for 10 days, they found no significant change in the ratio of villous height to total mucosal thickness. In contrast, Buchman *et al.*[1] showed a significant decrease in total intestinal mucosal thickness, van der Hulst *et al.*[2] a significant decrease in villous height and Guedon *et al.*[3] a significant decrease in microvillous height after 2–3 weeks of TPN.

Other studies have assessed intestinal digestive, absorptive and barrier function in patients receiving TPN. Nutritional support by TPN alone results in decreased intestinal mucosal brush border enzyme activity[3] and decreased amino acid transport by jejunal brush border membrane vesicles[4]. Buchman *et al.*[1,5] and van der Hulst *et al.*[2] have both shown an increase in intestinal permeability to lactulose in adults receiving TPN for a period of 2 weeks.

The differences between the results of Mr Sedman and colleagues and these studies may be due to the duration of TPN, and the methods used to express morphological parameters and assess intestinal barrier function. Sedman *et al.* used the ratio of villous height to total mucosal thickness to assess mucosal atrophy. According to the results of van der Hulst *et al.*[2], villous height was significantly reduced after 2 weeks of TPN whereas crypt depth was maintained. Therefore, using the villous height to mucosal thickness ratio may mask histological evidence of intestinal mucosal injury. Sedman and colleagues used bacterial translocation as evidence of gut barrier dysfunction. It should be noted that sampling for bacterial translocation in humans is usually restricted to a single mesenteric lymph node, intestinal serosal scrapings and venous blood sampling. This situation is in contrast with animal studies which may be more productive because of the relatively larger volume of tissue harvested, i.e. complete mesenteric lymph node complex, right lobe of liver, entire spleen and often a complete lung. Therefore, assessing bacterial translocation in humans may lead to an underestimate of the prevalence of gut barrier dysfunction in certain conditions.

What is the clinical significance of intestinal barrier dysfunction? It was interesting to note that infective complications after operation were more common in patients with evidence of bacterial translocation at laparotomy. This finding is similar to the authors' previous data in surgical patients undergoing laparotomy, in whom there was a higher incidence of septic complications in patients with bacterial translocation (28 per cent) compared with those without (11 per cent)[6]. Two other studies involving patients with burn injuries, in whom intestinal mucosal barrier function was assessed by measuring intestinal permeability to lactulose, demonstrated an association between gut barrier dysfunction and the later development of infective complications[7,8].

In adult humans, there is evidence that TPN for a period of 2–3 weeks is associated with intestinal mucosal atrophy, impaired intestinal absorptive and digestive function and intestinal mucosal barrier dysfunction. Impaired intestinal barrier function is associated with an increase in the incidence of infective complications.

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Author's reply

Sir

We are grateful to Mr Parks and colleagues for the interest shown in our paper. We agree that the differences in results obtained in our study compared to others may be a consequence of differing methods used to assess morphological parameters. However, we do not agree with their comments regarding villous height to mucosal thickness. This measure of villous atrophy is more accurate for the assessment of villous architecture than either independent variable[1]. Changes in villous height, for example, may occur because of a tendency to mucosal stretching during preparation of specimens. This fact has led other authors to question the value of such measures used in isolation[2]. The quoted paper by van der Hulst *et al.* is, therefore, of doubtful relevance in this regard. Interestingly, Guedon *et al.*, in contrast to van der Hulst but in accord with our results, found no effect with total parenteral nutrition (TPN) on villous height measured by light microscopy. The only morphological changes they found were minimal decreases in microvillous height on electron microscopy. Furthermore, these authors comment that the minor morphological modifications of the ultrastructure of the microvillus were not associated with changes in crypt depth. This finding is inconsistent with the hypothesis that there is a disturbance in enterocyte maturation as one might expect if these alterations were a consequence of the lack of luminal nutrients. The 'significant' decrease in intestinal mucosal thickness found by Buchman *et al.* was, in fact, a mean(s.d.) change from 645(17) to 512(27) μm in eight healthy volunteers aged between 25 and 34 years who received 14 days of TPN, before which all were fit and healthy and on normal diets. No other evidence of morphological changes were found in this study. The authors rightly concluded that alterations in villous architecture were mild and on any account were not related to changes in intestinal function or permeability. While it may be convenient to quote these papers as evidence to confirm an effect of TPN on mucosal morphology, it would seem premature to conclude that short periods of TPN have a clinically important deleterious effect on intestinal villous architecture.

The studies quoted by Mr Parks and colleagues commenting on alterations in intestinal digestive, absorptive and barrier function during TPN fail to point out the wide discrepancies that exist in published literature. This discrepancy is illustrated by simple appraisal of the studies they quote. For instance, Buchman *et al.* found no change in brush border enzyme activity while Guedon *et al.* did, although it is noteworthy that these authors conclude that 'the functional consequences observed during medium-term TPN in adults are probably limited'.

In our study we did not intend to use point prevalence of gut translocation as a measure of barrier function, as suggested by Mr Parks and co-workers. Our aim was to assess gut translocation in relation to mucosal morphology as there is powerful evidence of a causal association from animal experiments. Our results do not confirm this in human subjects receiving TPN. It is an appealing hypothesis that gut translocation will be increased in the presence of changes in permeability or other measures of intestinal function, but this was not the aim of the study.

The comments by Mr Parks and colleagues regarding lymph node sampling techniques were made in our discussion.

There is increasing evidence that the occurrence of gut translocation of bacteria is associated with an increase in septic morbidity, but the mechanism remains to be elucidated. As stated in our paper, it may simply be an epiphenomenon occurring in the immunocompromised individual who is already prone to sepsis. Patients receiving TPN may sometimes fall into this category. It would be inappropriate to conclude, however, that changes in mucosal architecture are a cause of translocation in patients receiving TPN. Furthermore, all experimental evidence available to date regarding changes in intestinal function and TPN suggests that any changes that do occur are of limited clinical relevance. We accept, however, that absence of evidence is not evidence of absence.

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Self-expanding metal stents for the palliation of dysphagia due to inoperable oesophageal carcinoma

Sir

Peroral stenting for palliation of oesophageal carcinoma is currently topical, and we read the article by Mr Ellul and colleagues (*Br J Surg* 1995; 82: 1678–81). The authors mentioned that they encountered tumour overgrowth in only two patients. In our early experience with the ultraflex prosthesis over the past 2 years, seven of 26 patients presented with recurrent dysphagia because of tumour overgrowth or ingrowth. This figure is in keeping with earlier series[1]. Dysphagia usually presented within 3 months of inserting the prosthesis.

To counter this event, we routinely pursue a policy of monthly endoscopic surveillance of patients with the Strecker (Microvasive Boston Scientific, Watertown, Massachusetts, USA) stent, when any tumour excrescences are injected with absolute alcohol. Better control is achieved by this method than by dealing with the problem when patients present with dysphagia. The authors also mention that tumour tissue that grows through the stent mesh is exceedingly friable and can be brushed away by the endoscope. This is not so in our experience.

We do not routinely perform a contrast swallow before stent insertion, and dilatation has been necessary in only one patient.

Oesophageal stents provide palliation and survival benefits similar to laser therapy[2]. No trials have been done comparing laser therapy with absolute alcohol injection. Coated stents may be the way ahead; they can prevent the ingrowth of tumour, but stability is said to be affected and the risk of stent migration is present.

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Use of a semipermeable polyamide dressing over skin grafts to venous leg ulcers

Sir

I found the paper by Messrs Mahajan and Mosley (*Br J Surg* 1995; 82: 1359–60) interesting and informative. However, I would like to know on what scientific grounds they can make a statement that conventional dressings applied to skin grafts have to be left undisturbed for 7 to 10 days to allow the graft to anchor. It is my non-scientific experience that grafts have taken with good 'stickability' within 24 to 36 hours of application.

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Book reviews

Nerve Injuries. Operative Results for Major Nerve Injuries, Entrapments and Tumors

D. G. Kline and A. R. Hudson. 265 × 187 mm. Pp. 611. Illustrated. 1995. Philadelphia, Pennsylvania: W. B. Saunders. £100.

Peripheral nerve injury is not generally considered to be one of the glamour topics of surgery, and the management of such injuries tends to fall between plastic, orthopaedic and neurosurgeons, with only a few people taking a real interest in the subject. The authors of this book are two world-renowned authorities who have, over the past 25 years, built up enormous experience in the field. This volume passes on that experience, including a full discussion of results. The first quarter of the book covers basic physiology and pathology, clinical examination and investigations, and an overview of operative techniques. The bulk of the rest of the book is then dedicated to individual nerves or nerve groupings. Despite the title, more than just injuries are covered, including entrapment syndromes and tumours. Although the personal element is emphasized, there is also discussion of controversies within the subject, and references are comprehensive. The book has many strengths and no great weaknesses. It is clearly written and, by emphasizing their personal approaches, the reader does not become overwhelmed by differing points of view. The operative descriptions are excellent, but the most impressive feature of the book are its illustrations. There are very clear operative photographs, both in black and white, and colour, backed up in places with excellent line drawings. Anybody who deals with trauma, within whichever discipline they practise, should read this book and it should be available in all orthopaedic, plastic and neurosurgical departmental libraries.

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Reconstructive Surgery of the Lower Genito-Urinary Tract in Adults

S. Colleen and W. Månsson (eds). 241 × 158 mm. Pp. 268. Illustrated. 1995. Oxford: Isis Medical Media. £49.95.

This book is part of an initiative by the International Society of Urology (SRU) to offer regular updates to a wide audience on important topics within urological practice. It is the ninth in the series and its contents are derived from a session held at the 23rd SRU Congress in 1994.

The book comprises 24 chapters arranged in five parts. It is written by internationally renowned and well respected leaders in the field of reconstructive surgery. It follows a logical pattern, starting with preoperative assessment followed by four sections that include reconstruction of the bladder (including urinary diversion), urethra, penis with male reproductive tract and, finally, the female urethra (including fistula). I found all chapters to be generally well written in a readable style and to be comprehensive in a field which is wide and expanding rapidly. Especially welcome was the initial emphasis on proper preoperative assessment, which reinforced once again that the skills of the surgeon are not only technical; patient selection, counselling and assessment are also important. Perhaps more diagrams and illustrations could have been included in some of the chapters, but those by Fitzpatrick, Hauri and Blavius were particularly good in this regard.

Overall I found the text easy, enjoyable and interesting reading. This volume is suitable for anyone interested in reconstruction of the lower urinary tract, including paramedical staff. It is especially suited to those in training.

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Tissue Approximation in Endoscopic Surgery

A. Cuschieri and Z. Szabo. 284 × 222 mm. Pp. 181. Illustrated. 1995. Oxford: Isis Medical Media. £74.95.

This book serves as an encyclopaedia of sutures, needles, knots, knot-tying techniques and instruments to be used particularly in laparoscopic surgery. It deals with knotting in the first section and suturing during laparoscopic surgery in the second section. It has a large number of didactic, schematic figures supported by text. In most instances possible variations are described, as are common pitfalls. The illustrations by Derek West are of very high quality and serve as a step-by-step manual. This book should be of great interest for anyone considering performing more advanced laparoscopic surgery than uncomplicated laparoscopic cholecystectomy. This area has been developing rapidly during the past couple of years and there is a strong need for a book assimilating appropriate information, evaluating the different techniques and, by step-by-step illustration, describing useful techniques. This volume serves this purpose well. It should be included in the clinical library in every institution with responsibility for surgeons in training. In addition, many surgeons considering more advanced laparoscopic surgical procedures would find this text to be a useful component of their private medical library.

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Clinical Anatomy for Laparoscopic and Thoracoscopic Surgery

R. Savalgi and H. Ellis (eds). 253 × 193 mm. Pp. 325. Illustrated. 1995. Oxford: Radcliffe Medical Press. £95.

This nicely produced book sets out to fulfil one of the needs of the laparoscopic surgeon: understanding anatomical detail from a new aspect. It covers the anatomy of the abdomen and groin, thorax and the gynaecological organs.

There are conventional anatomical chapters on the abdomen, chest, groin, pelvis and related organs but, although these are clear and well written, they are disappointing in that they fail to point out areas of anatomy important to laparoscopists. There is nothing about the anatomical dangers encountered when inserting port sites, or advice about positioning port sites to obtain the best view of deep structures. There is a useful chapter on laparoscopic ultrasonography. The best parts of the book are the anatomical chapters co-authored by a surgeon experienced in surgical as well as anatomical problems. These include chapters on the biliary tract, oesophagus, hiatus, stomach, spleen, suprarenals, colorectal tract and cadaveric dissections of the inner aspect of the groin. There are four chapters on thoracoscopic surgery which contain little that is new. A short, very clear chapter on thoracoscopic sympathectomy might be improved by a craniocaudal diagram of the connections of the sympathetic chain to explain the anatomical basis of this operation. Finally there are two chapters on robotics and virtual reality imaging. These make exciting reading and show how a precise understanding of anatomy is going to be even more important in the future.

Overall this is a good book which many laparoscopic surgeons will find useful to have on their bookshelves.

D. C. Dunn

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Hamilton Bailey's Emergency Surgery. 12th ed.

B. W. Ellis (ed.). 282 × 222 mm. Pp. 866. Illustrated. 1995. Oxford: Butterworth-Heinemann. £95.

Textbooks of emergency general surgery are not usually written for consultants but for juniors. This one, with 38 contributors to 66 chapters, should interest all consultants in the acute specialties; its database is set at a suitable level for all training grades and, because it is simply and well written, it might also be suitable for medical students who would learn something other than lists and abbreviations from a pocket book. In the UK National Health Service emergencies will form the main work of the future and it is a problem to decide how junior staff should be trained. First of all they should arm themselves with the two books of Hamilton Bailey's legacy *Short Practice of Surgery* and this one. They are complementary, not exclusive. This one contains chapters by such leading surgeons as Wolfe, Birch and Helal written to the correct level without an unnecessary cookbook type of approach for operations which should be done by ultraspecialists. There is an excellent chapter on 'primary care of the injured' by Snook including details on how a doctor should proffer help at the scene. He emphasizes the importance of assessing the accident and the kinetic energy involved. General principles (the first 12 chapters) are described sensibly, with organized knowledge rather than a mass of information.

The specialist chapters cover their subjects well. The only imbalance is the lack of information on fractured pelvis, which curiously appears in Abercrombie and Payne's chapter on urology, because the kinetic energy needed to break the pelvis involves other organs. Fractured pelvis is the leading cause of death from fracture. Incidentally, orthopaedics has 75 pages compared with 71 for urological emergencies. This book review is a little longer than average for *The British Journal of Surgery* because emergency surgery is an extremely important topic. It is not actually a rapidly changing field which needs yearly updating, but the ground needs tilling regularly and the generality of acute emergency surgery continuously emphasized. Buy the 12th edition of *Hamilton Bailey's Emergency Surgery* and hunt for the first; it was equally as good.

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British Journal of Surgery 1996, 83, 718

Notices and announcements

7–10 May 1996
Research Methods in Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

16–17 May 1996
International Symposium on Breast Reconstruction
Chester, UK
Information: D. McGeorge, Department of Plastic and Reconstructive Surgery, Countess of Chester Hospital, Chester CH2 1UL, UK

20–22 May 1996
Trauma and Critical Care '96 - Point/ Counterpoint XV
Boston, Massachusetts, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

22–24 May 1996
Association of Surgeons of Great Britain and Ireland Annual Meeting
Glasgow, UK
Information: Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

22–25 May 1996
25th Meeting of the European Histamine Research Society
Antwerp, Belgium
Information: G. Van de Vyver, Department Geneeskunde, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium

30 May–1 June 1996
Surgical Infection Society — Europe
Paris, France
Information: Professor P. Frileux, Scientific Secretariat, Department of General Surgery, Hôpital Laennec, 42 rue de Sèvres, 75007 Paris, France

6–7 June 1996
Head and Neck Course 1996 — Hypopharyngeal Cancer
Hong Kong
Information: Head and Neck Course Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

7 June 1996
Difficult and Controversial Issues in Vascular Surgery
Saltash, Cornwall, UK
Information: Mr S. Ashley, Vascular Surgical Unit, Derriford Hospital, Plymouth PL6 8DH, UK

12–15 June 1996
International Association of Pancreatology
Mannheim, Germany
Information: Mr A. L. Warshaw, IAP Secretary, Massachusetts General Hospital, 15 Parkman Street, WAC 336, Boston, Massachusetts 02114, USA

16–22 June 1996
38th Annual World Congress of the International College of Angiology
Köln, Germany
Information: D. M. Rossignol, Executive Director, International College of Angiology, 5 Daremy Court, Nesconset, New York 11767, USA

23–26 June 1996
4th International Congress of the European Association for Endoscopic Surgery
Trondheim, Norway
Information: Congress–Conference A/S, PO Box 7609 Skillebekk, N-0205 Oslo, Norway

26–29 June 1996
CAR'96 – Computer Assisted Radiology 10th International Symposium and Exhibition
Paris, France
Information: Professor H. U. Lemke, Technical University Berlin, Institute for Technical Informatics, Sekr. CG FR 3-3, Franklinstrasse 28–29, D-10587 Berlin, Germany

27–28 June 1996
Surgical Research Society
Birmingham, UK
Information: Ms L. Hopwood, University Department of Surgery, Royal United Hospital, Bath B15 2TH, UK

29 June–3 July 1996
7th Annual Training Course for Clinicians: Practical Nutritional Support
Southampton, UK
Information: Mr B. Moran, Institute of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton SO16 7PX, UK

5–6 July 1996
Current Status of Surgical and Interventional Procedures for the Management of Aortic Aneurysm, Reno-Vascular Disease and Carotid Stenosis
Stratford-upon-Avon, UK
Information: Mrs L. de Cossart, Consultant Surgeon, Countess of Chester Hospital, Liverpool Road, Chester CH2 1UL, UK, or Dr J. Dyet, Consultant Radiologist, Hull Royal Infirmary, Anlaby Road, Hull HU3 3KZ, UK

7–9 July 1996
Joint Meeting of British Oncological Association in association with Royal College of Radiologists, British Institute of Radiology and British Society for Cell Biology
Cardiff, UK
Information: Meeting Secretariat, BOA 1996, 4 Cavendish Square, London W1M 0BX, UK

8–10 July 1996
Tripartite meeting of the Association of Coloproctology of Great Britain and Ireland, Section of Coloproctology of the Royal Society of Medicine, American Society of Colon and Rectal Surgeons, Section of Colon and Rectal Surgery of the Royal Australasian College of Surgeons, Colorectal Surgical Society of Australia
London, UK
Information: Confrex, Conference Secretariat, 145 Islingword Road, Brighton, Sussex BN2 2SH, UK

8–10 July 1996
Association of Coloproctology Tripartite Meeting
London, UK
Information: Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

11–12 July 1996
British Association of Surgical Oncology Summer Scientific Meeting
Oxford, UK
Information: Mrs V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 July 1996
Hong Kong Surgical Forum – Summer 1996
Hong Kong
Information: Forum Secretary, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

4–8 September 1996
International Congress of Phlebology
Corfu, Greece
Information: Professor P. Balas, 4 Hiraclitou Street, Athens 10673, Greece

6–8 September 1996
6th National Conference of the Indian Association of Surgical Gastroenterology
New Delhi, India
Information: Professor T. K. Chattopadhyay, Secretary, IASG, Department of Surgery, All India Institute of Medical Sciences, New Delhi 110029, India

Instructions to authors

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An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** In order to avoid subsequent embarrassment, authors are requested to submit with their manuscript copies of any other papers, either published, in press, or submitted for consideration elsewhere, which relate to the same subject. It is essential that publications or submissions using the same data set should be submitted to the Editors to allow assessment of any potential overlap with the submission to the Journal. The title page should indicate whether the paper is based on a previous communication to a society or other meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

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These describe technical innovations or modifications that may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

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The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. This should clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. It should embody the purposes of the study or investigation, basic procedures (study material, and observational and analytical methods); main findings (with specific data and their statistical significance) and the principal conclusions. The summary should be written in clear prose.

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b

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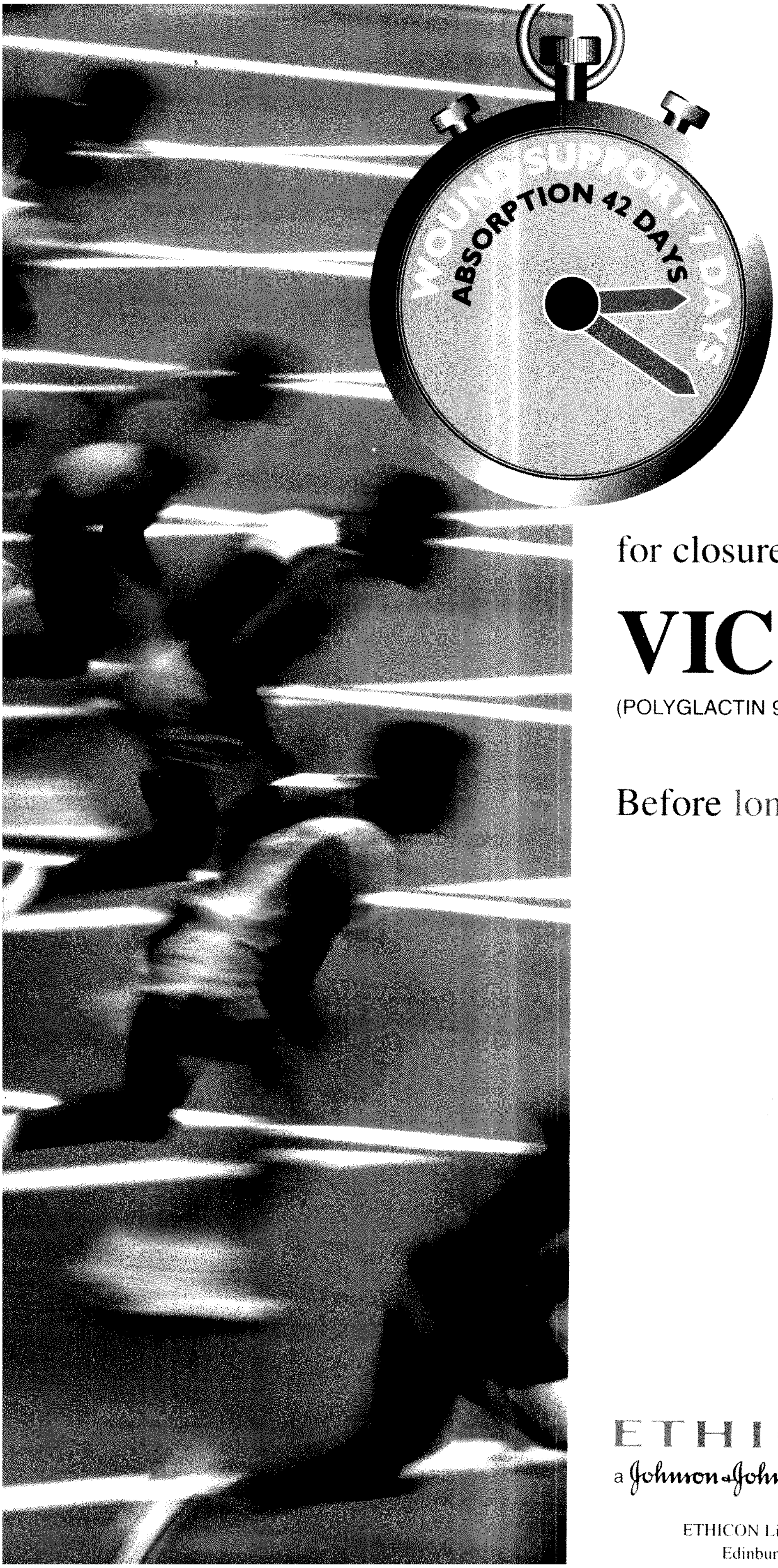

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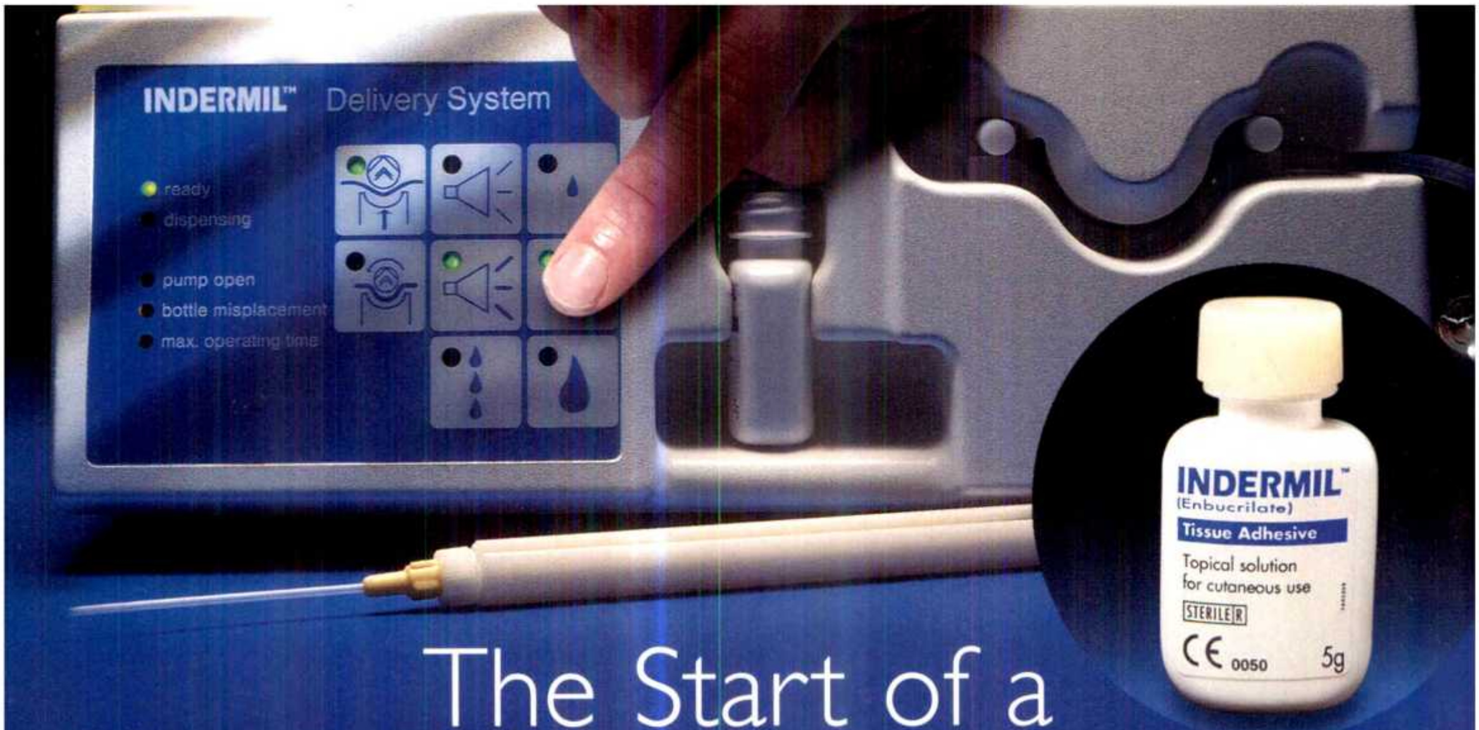

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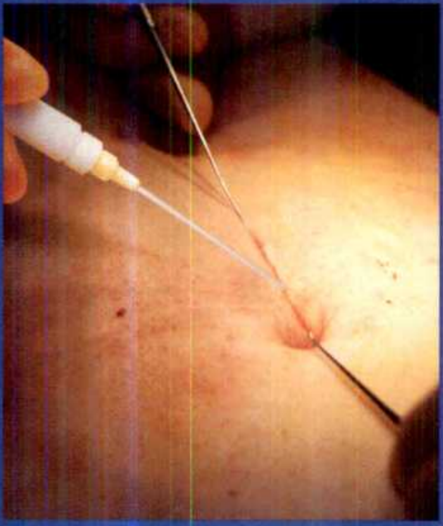

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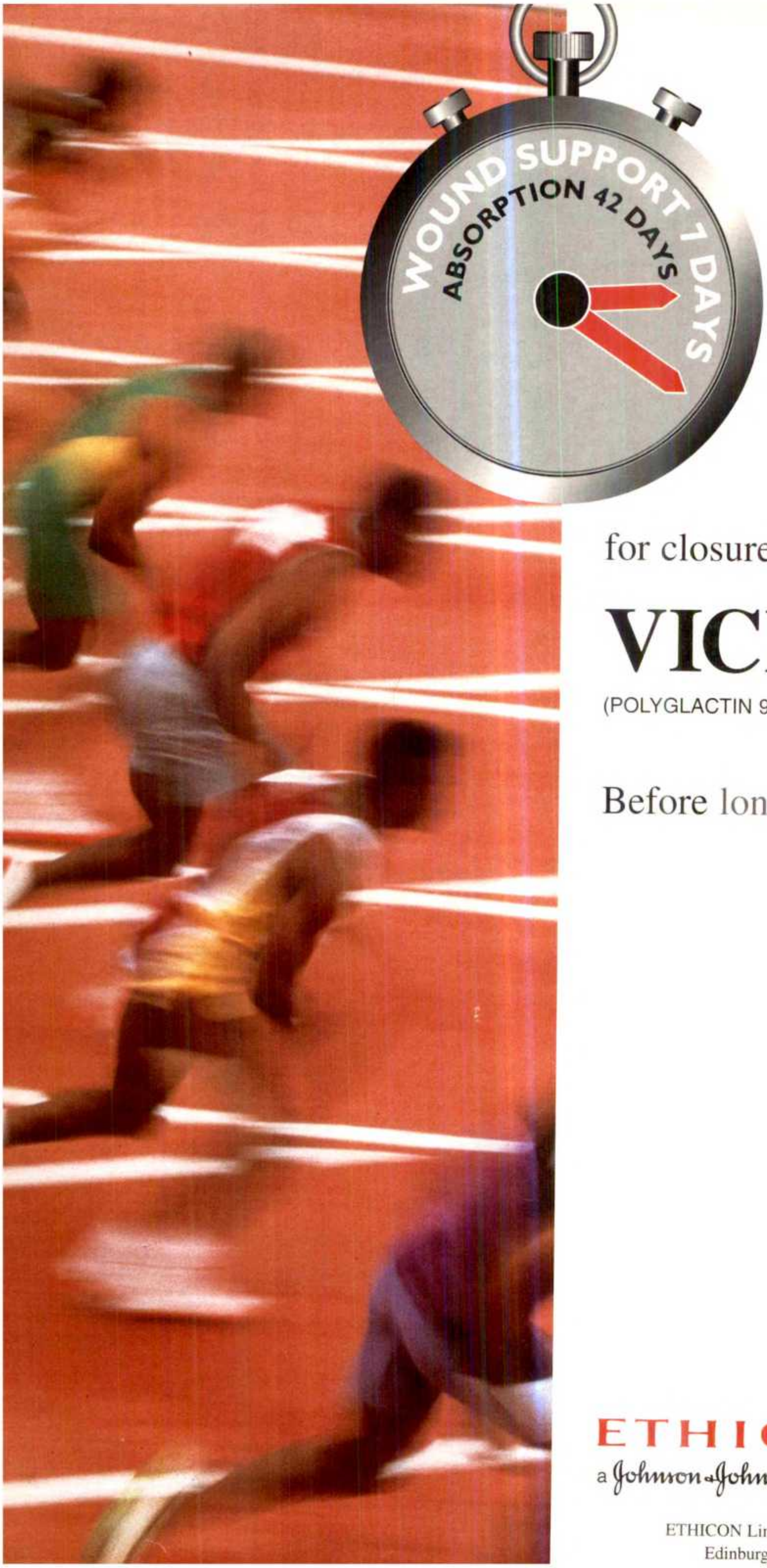
ISSN 0007-1323

Typeset by Unicus Graphics Ltd
Printed by The Friary Press



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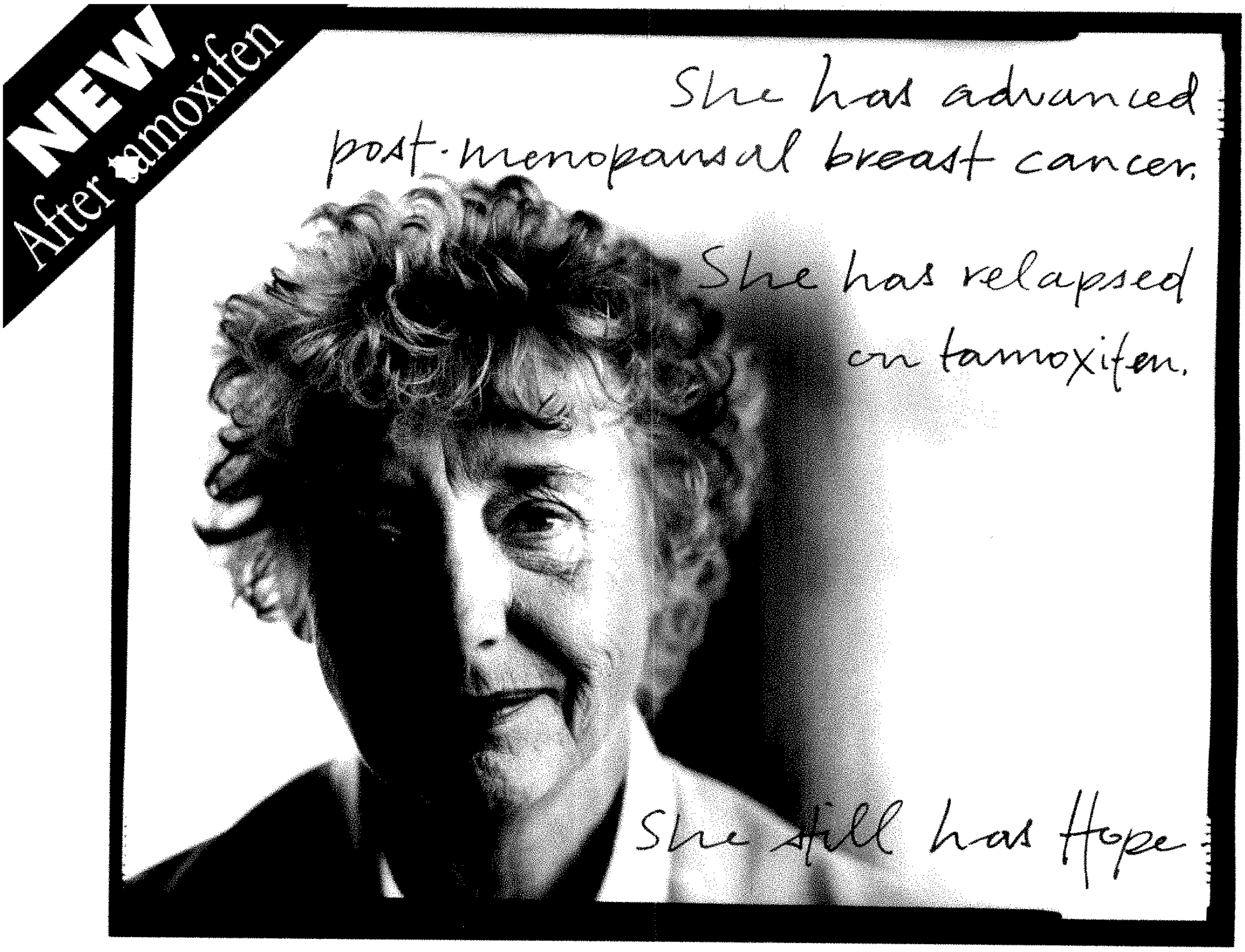
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Leading articles

Laparoscopic adrenal surgery

The surgical management of patients with adrenal disease depends on the functional nature of the endocrinopathy and the preference of the surgeon for one of the various surgical approaches: anterior transperitoneal and thoracoabdominal incisions, extraperitoneal flank incisions and the posterior approach. All these conventional approaches have in common a requirement for long incisions. The flank or posterolateral retroperitoneal routes offer direct access to the adrenal but have the disadvantages associated with the need to remove the 11th or 12th rib, with the potential danger of injury to the pleura and the intercostal nerves causing, in some patients, chronic pain syndromes. The principal source of morbidity associated with open adrenalectomy is related to the access required to remove the tumour.

Adrenalectomy is ideally suited to minimally invasive surgery based on the well defined blood supply of the adrenal and the characteristics of the tumours, which are usually small and benign. However, the partially retrocaval and retrohepatic location of the right gland and the para-aortic, retropancreatic and justasplenic position of the left, means dissection is not always easy; sometimes the distinction between the perirenal and the periadrenal fat and the adrenal gland may be difficult on the basis of colour differences.

With these advantages and disadvantages in mind, Gagner *et al.*[1] in 1992, and subsequently other groups[2–5], reported clinical success in the surgical management of a variety of benign non-functional and functional adrenal tumours, including pheochromocytoma. In the majority of the reports carbon dioxide was used to create pneumoperitoneum. In general, insufflation of carbon dioxide during endoscopic surgery results in an increase in its partial pressure and a fall in arterial pH. In most healthy patients the rise in carbon dioxide causes no significant physiological stress; however, in patients undergoing long-lasting procedures and in those with pre-existing cardiorespiratory disease there is a rise in carbon dioxide level. Hypercarbia affects the cardiovascular system, resulting in myocardial depression and arteriolar dilatation, and an increase in myocardial oxygen consumption caused by the release of catecholamines[6]. Also, pneumoperitoneum produces haemodynamic changes, such as an increase in heart rate and mean arterial pressure; these are independent of the insufflation agent. These features must be considered in patients with pheochromocytoma, even with adequate adrenergic receptor blockade, and careful perioperative respiratory and cardiovascular monitoring. To minimize, in part, all the changes associated with carbon dioxide pneumoperitoneum, we have successfully used helium in patients with unilateral and bilateral pheochromocytoma[7]; this method deserves further investigation.

The supine half lateral position allows a careful laparoscopic exploration of the entire abdominal cavity. This can be useful in some patients to exclude the presence of another pheochromocytoma. It also allows total bilateral adrenalectomy without the need for changing sides and repositioning of the patient. However, most laparoscopic surgeons favour the lateral decubitus position. This approach allows a direct route to just one gland but it requires less dissection than the anterior approach.

Recently, laparoscopic surgeons have moved to an extraperitoneal approach in which space is created by the introduction of a trocar with an inflatable balloon tip. This technique has the advantages of a minimal access procedure together with direct access to the adrenal gland without interference with the intraperitoneal organs. Moreover, extraperitoneal carbon dioxide insufflation may be safer than pneumoperitoneum in patients with pre-existing cardiorespiratory disease and in those with pheochromocytoma, providing more haemodynamic stability. The main disadvantage of the retroperitoneoscopic approach is its restricted working space, leading to a difficult dissection when the adrenal tumour is more than 5 cm in diameter; in this situation the surgeon can switch from a complete retroperitoneal approach to a combined retroperitoneal and transperitoneal endoscopic operation. Future studies are needed to compare these two laparoscopic approaches. We believe the extraperitoneal approach is suitable for small tumours and in obese patients with Cushing's syndrome.

It has been said that the introduction of the laparoscope into the field of general surgery has changed the specialty forever, but it is an important principle of minimally invasive surgery that no surgeon should undertake a laparoscopic procedure unless he or she can perform that procedure on an open basis, with some degree of expertise. Adrenal surgery should be left in the hands of general surgeons who have a special interest in endocrine surgery. Endocrine surgeons who do not frequently undertake abdominal surgery, such as laparoscopic cholecystectomy, should be encouraged to obtain training in laparoscopic techniques if they wish to maintain a leading role in this sphere.

In all surgical series, laparoscopic adrenalectomy has been associated with excellent results, with a conversion rate of less than 5 per cent, no deaths and very low morbidity rates[8]. However, no prospective clinical trials have yet compared open and laparoscopic methods. Prinz[9] recently reported a retrospective study comparing conventional transabdominal and posterior methods with a laparoscopic approach in patients with unilateral tumours. Adrenalectomy took longer to perform via the laparoscope than via the conventional open approaches, but the laparoscopic method had the advantage of reducing postoperative hospital stay and analgesic requirements. This particular form of laparoscopic surgery is now well established throughout the world, but future clinical trials with adequate follow-up should assess results for specific adrenal disorders.

Absolute contraindications to laparoscopic adrenalectomy have not yet been established; relative contraindications may depend on the knowledge, skill and experience of the surgeon. However, many operators believe that lesions over 10 cm in size which are likely to be malignant are probably not appropriate for laparoscopic resection[9].

In conclusion, after a limited experience of laparoscopic adrenalectomy surgeons have found that it causes less discomfort for the patient; the laparoscopic technique is, in essence, similar to open resection via the intraperitoneal or retroperitoneal route. Open adrenalectomy gives optimal access and has known long-term results. However, Cuschieri[10] has drawn attention to the trauma ratio 'surgical procedure: access'. Total operative trauma consists of the trauma of access and exposure of the relevant anatomy, and the actual trauma inherent in the procedure itself. For the majority of patients with benign adrenal tumours conventional open access trauma comprises a considerable component of the total operative insult. In such circumstances minimal access laparoscopic techniques should be preferred.

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Announcement

National Confidential Enquiry into Counselling for Genetic Disorders. Medullary thyroid carcinoma/multiple endocrine neoplasia type 2 audit, 1990–1991

This report to the Department of Health has now been published. Copies are available, free of charge, from the following address:

Royal College of Physicians of London, Genetic Enquiry Centre, St Mary's Hospital,
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British Journal of Surgery 1996, 83, 724–725

Leading articles

Cholangiography and laparoscopic cholecystectomy

The demonstration of stones in the common bile duct by cholangiography is a prerequisite for their successful removal. Routine operative cholangiography was normal practice at open cholecystectomy; the logical extension of the change from open to laparoscopic surgery is that routine operative cholangiography followed by laparoscopic bile duct exploration should be the method of choice. Currently, however, most surgeons seem to prefer endoscopic sphincterotomy for clearance of bile duct stones, a method associated with definite morbidity and a very low mortality rate. Routine endoscopic retrograde cholangiopancreatography (ERCP) before every cholecystectomy is neither necessary nor acceptable.

Before the laparoscopic revolution of 1989–1990 the case for selective cholangiography was well made[1,2]. Few clinically important bile duct stones are missed if a dilated bile duct, multiple gallbladder stones, pancreatitis or jaundice are considered as indications for cholangiography. Laparoscopic surgery does not usually allow easy or accurate measurement of bile duct diameter to be made at operation, so weakening this case. With these clinical criteria, the number of patients undergoing cholecystectomy who have unexpected bile duct stones varies widely between studies, but might be predicted to be a little over 5 per cent[3]. Conversely, when duct stones might be predicted, radiological imaging is positive in under 50 per cent of cases. It is, therefore, desirable to have a better assessment of the bile duct than that available from reliance on clinical indicators.

Preoperative ERCP has the advantage of allowing the simultaneous treatment of duct stones. Even if it is used selectively, however, many negative examinations are performed and, if there are no stones, the patient still runs a low risk of pancreatitis[4]. Most patients undergoing laparoscopic cholecystectomy are relatively young. If stones are found, the lower biliary sphincter is destroyed to treat them; this is a new departure in the treatment of duct stones in young people.

Laparoscopic operative cholangiography has been avoided because of perceived difficulty with the technique and a desire to reduce the duration of laparoscopic cholecystectomy. If stones are found, the surgeon must either convert to open duct exploration, a comparatively safe but now unfashionable approach, or explore the duct laparoscopically, a skill that few surgeons have yet so far acquired. There is a low risk of injury to small bile ducts at operative cholangiography[5]. Alternatively, the stones may be left for postoperative removal by endoscopic sphincterotomy. For the latter to be a valid option the success rate needs to be 100 per cent[4]; this standard is rarely achieved[6], making endoscopic sphincterotomy a poor alternative. The attendant disadvantages of risk and biliary incontinence also exist.

A preoperative knowledge of the state of the bile duct is helpful but the two approaches outlined have significant disadvantages; fortunately, they can be refined. Two strategies using intravenous cholangiography or ultrasonographic measurement of the duct diameter are available. Ultrasonography has the advantages of simplicity, universal availability, rapidity and the avoidance of radiation. Combined with the use of biochemical liver function tests it is almost 100 per cent accurate in excluding duct stones. A dilated duct means that further evaluation is required. In Southmead Hospital, Bristol, this method has resulted in very few extra ERCP procedures being performed and only four patients presenting with probable missed stones in 600 cases.

Intravenous cholangiography has the advantage over ultrasonography of directly visualizing the duct and, potentially, determining absolutely the presence or absence of duct stones. Failure of opacification occurred in 10 per cent of cases in one of the studies reported in this issue of the Journal and in 2·7 per cent in the other[7,8]. This difference is probably accounted for by the different timing of the studies; the more recent one also had better specificity and fewer reactions to contrast agent. The technique takes substantially longer than ultrasonography and uses radiation. While improvements in intravenous cholangiography make it a useful occasional alternative to ultrasonographic assessment of the bile duct, time, cost and occasional failure, together with the low risk of allergic reaction, make it less attractive. Nevertheless, whatever the technique used, if endoscopic sphincterotomy is to be the therapeutic option for duct stones, preliminary assessment for high-risk patients offers a reduction in the number of (unnecessary) ERCP procedures.

Many duct stones migrate through the biliary sphincter; any assessment of the bile duct is valid for only a short time and must be made close to the date of operation. If repeated examinations are required, ultrasonographic measurement of bile duct diameter is an excellent choice, complemented by biochemical tests of liver function.

In practice there are several assessment options available but two appear most attractive. The first is selective operative cholangiography based on preliminary ultrasonography, followed by laparoscopic cholecystectomy and duct exploration if required. An obvious benefit of this method is the ability to deal with the whole stone problem simultaneously, leaving an intact sphincter. Available results are few and must be regarded as preliminary, but they show promise. For the future, laparoscopic ultrasonography will measure bile duct diameter[9] and, if this is normal, no further action other than removal of the gallbladder will be needed. If the duct is dilated but incompletely visualized, contrast cholangiography may be performed. The second option is ultrasonographic assessment followed by ERCP and sphincterotomy, if indicated, with subsequent laparoscopic cholecystectomy.

At present, neither option is clearly or universally superior. Local expertise will vary in both the methods of assessment and those of treatment. In any event, the difference in outcome is likely to be tiny. Perhaps increasing experience with laparoscopic bile duct exploration will determine the favoured method with the passage of time.

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British Journal of Surgery 1996, 83, 726–733

Review

Strategies to decrease the incidence of intra-abdominal recurrence in resectable gastric cancer

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Two main approaches are suggested to improve treatment results in resectable gastric cancer: extended lymphadenectomy and adjuvant antitumour therapy. Progress is to some extent stalled by the perception of gastric cancer as a pathophysiologically uniform disease; it has been demonstrated, however, that there are variants of gastric cancer associated with predominantly intra-abdominal spread or with haematogenous metastases. Recent clinicopathological studies have provided information about the mechanisms of this metastatic diversity. A review of clinical trials suggests that no single method of treatment can efficiently address all variants of gastric cancer spread, but new treatment strategies may be based on defining the pathophysiological variant of gastric cancer and selecting adjuvant therapy according to the most probable mode of tumour spread. Treatment should start with surgery which includes a 'reasonably' extended lymphadenectomy aimed at achieving an increased rate of curative resection and more accurate staging. Risk factors for peritoneal spread of tumour require the perioperative use of intraperitoneal chemotherapy. Subsequent adjuvant therapy may be indicated in patients at high risk of further cancer spread or occult metastases, as determined by pathological examination of the resected specimen.

Definition of the problem

The long-term results of treatment for resectable gastric cancer have shown no significant improvement in recent decades[1]. In Japan, the 5-year survival rate is two to three times higher than that in Western countries. This East–West discrepancy has not been definitely explained, but some authors attribute it to a more systematic approach to surgery and more extensive surgical treatment in Japan[2]. In the study conducted by the American College of Surgeons[3], it was found that 'gastric and perigastric nodes' were dissected in 47–49 per cent of patients treated with curative intent, while the greater omentum, a major site of gastric cancer peritoneal spread, was resected in 41 per cent of cases. While Eastern clinical investigations were aimed at improved cancer surgery, in the West considerable efforts were made to develop adjuvant intravenous chemotherapy. Meta-analysis of randomized trials[4] as well as analysis by Wanebo and colleagues[3] failed to demonstrate any advantage for the latter treatment strategy.

According to Japanese researchers, peritoneal surfaces and the liver[5–7] are the major sites of treatment failure after D_{2-3} resection (dissection of the lymph nodes of N_2 and N_3 groups). However, in the USA[3] first recurrence after curative surgery is locoregional in 40 per cent of cases. Among the sites of treatment failure in patients included in adjuvant therapy protocols evaluated by the Gastrointestinal Tumor Study Group were liver, peritoneum and the gastric bed[8]. More recently, Wils and colleagues[9] reported a similar pattern of recurrence after analysis of trials utilizing neoadjuvant chemotherapy. The purpose of this article is to review the accumulated clinical data on intra-abdominal recurrence of resectable gastric cancer and to suggest a strategy that may decrease this incidence.

Paper accepted 24 November 1995

Patterns of dissemination

Gastric cancer advances along several routes: lymphatic, haematogenous, by direct extension and transcoelomic. In a significant proportion of cases it also disseminates simultaneously by several routes, creating a mixed pattern of treatment failure that is considered characteristic of the disease. However, isolated sites of surgical treatment failure do occur. Careful studies of recurrence by anatomical region show that in about 50 per cent of patients local and/or intra-abdominal disease are the only sites of first recurrence after curative surgery and even at death tumour remains confined to the abdomen[10–12]. Evaluation of clinical and autopsy studies demonstrates that intra-abdominal spread of the tumour (local recurrence, liver metastases and peritoneal seeding) is the major feature of both single and multicomponent metastatic processes following radical surgery[10–19]. Extra-abdominal, haematogenous or lymphatic spread without intra-abdominal metastases occurs rarely. The concept of gastric cancer as a disease with early systemic dissemination is not supported by these clinical studies. Rather it should be regarded as a disease with early intra-abdominal spread, associated over time with an increasing incidence of distant metastasis.

More than 50 per cent of all recurrences take place within 2 years of surgery and only about one-third between the third and fifth years[13,14,16]. The incidence of local and extra-abdominal metastases is the same in the 'early' and 'late' relapse groups. In contrast, peritoneal dissemination and liver metastases are more often encountered in the group with 'early' recurrence (within 2 years of surgery)[13,14]. Koga and colleagues[14] showed that liver metastases tend to occur earlier (81 per cent within 2 years), while lung and bone metastases occur later (66 per cent after the second year of follow-up). This finding may support the concept of 'key disseminating sites'[20]. This hypothesis holds that these sites of recurrence must first be seeded by primary tumour and then provide for further cancer dissemination. Weiss[21] defined this as a stepwise progression of cancer.

Influence of gastric cancer histology on the pattern of treatment failure

Clinicopathological studies reveal that the overall incidence of gastric cancer metastases in abdominal lymph nodes is 60–80 per cent, on the peritoneal surfaces 30–50 per cent and in the liver 25–40 per cent. Evaluation of surgical failures may be less helpful in the development of new treatment strategies if results are analysed with all patients with gastric cancer considered as a single group. Numerous clinicopathological studies have demonstrated by multivariate analysis that tumour stage is the most significant prognostic factor. While stage of disease may be the best prognosticator for patients with gastric cancer as a group, it may not provide as much information about an individual patient's prognosis. Also it does not help in modifying treatment strategy according to the most probable site of subsequent treatment failure.

In 1965 Laurén[22] introduced a histological classification of gastric cancer, recognizing intestinal, diffuse and intermediate types. Several other classifications have been suggested, such as expanding and infiltrative types[23], and glandular and non-glandular types[24]. Subsequent studies clearly show that these types of gastric cancer are associated with different epidemiology, precancerous conditions, gross morphology, patterns of spread and prognosis.

Evaluation of the metastatic patterns of these tumour types shows that the incidence of lymph node metastases is independent of tumour type and is related to the level of tumour invasion. On the other hand, the incidence of liver metastases and peritoneal dissemination is consistently different between histological tumour types; these differences remain, no matter which classification is used[25–30]. Liver metastases are found more often in patients with intestinal and corresponding tumour types (50–70 *versus* 3–30 per cent for the diffuse type). Peritoneal seeding is a characteristic feature of the diffuse type (45–75 *versus* 10–30 per cent for the intestinal type).

Molecular and immunohistochemical studies

Immunohistochemical studies of cell adhesion molecules confirm that two major types of gastric cancer are significantly different in their biological properties. Several of these molecular markers show variable expression in different types of gastric cancer.

Nakamura and colleagues[31] demonstrated the correlation of basement membrane status with degree of tumour differentiation and survival. Fragmentary or unrecognizable types of laminin and collagen type IV distribution were encountered in tumours with poor or moderate differentiation and infiltrative growth pattern that are associated with poor survival. On the other hand, noticeable expression of these molecules was a characteristic of differentiated tumours associated with better survival. The expression of E-cadherin was studied in primary tumour and its intra-abdominal metastases by Mayer and co-workers[32]. Intestinal type of tumour has a greater expression of E-cadherin in both primary and metastatic gastric cancer, especially in the liver. Diffuse type is characterized by extremely low or no expression of E-cadherin, both in the primary tumour and its metastases. A similar association of liver metastases with E-cadherin expression by gastric cancer cells was reported by Shiozaki and colleagues[33]. CD44, a receptor regulating cell–cell interaction, is overexpressed in primary tumours and metastases. Expression of CD44 is different in well and poorly differentiated types of gastric cancer; peritoneal spread is more frequent in the latter type[34]. Genetic changes are also found to be of considerable significance in the multistage progression of gastric cancer and different patterns of dissemination. Differences in oncogenes and tumour suppressor gene alterations[35] observed in the two types of gastric cancer suggest that intestinal and diffuse types may have different genetic pathways.

Mechanisms of local recurrence

The majority of local recurrences after putatively curative surgery for gastric cancer occur because of inadequate resection of the stomach, adjacent structures and/or lymph node metastases at the resection site. Another source of intra-abdominal recurrence is tumour cells that exfoliate from the serosal surface before or during resection in at least 30 per cent of cases. These free intraperitoneal cancer cells have been shown to be viable, and able both to implant and to proliferate[36–38]. Implantation takes place within minutes and the cells cannot subsequently be dislodged by irrigation[39]. Adherence of gastric cancer cells to mesothelium has been linked to the adhesion molecule CD44[40], as well as to substrate sugar chains on the cancer cell surface and α-fucosyltransferase on the mesothelial cell surface[41]. Adherence of cancer cells to peritoneal surfaces may be facilitated by surgical trauma and subsequent wound healing. During the early stages of wound healing, plasma proteins extravasate and form deposits that trap tumour cells[42,43]. In their turn, tumour cells express the family of receptors known as integrins, facilitating their attachment to these proteins[44]. Attached tumour cells may be assisted to implant and progress by the plethora of cytokines and growth factors secreted at the wound site. The fibrin deposits and the connective tissue matrix may act as a protective coat, shielding the neoplastic cells from an antitumour immunohistological response and from direct contact with even intraperitoneally administered drugs. These events are summarized in the hypothesis of 'tumour cell entrapment' which may be important in our understanding of the mechanism of both resection site and peritoneal surface recurrence[45].

Role of surgery

Although conflicting opinions continue to be published regarding the value of extended lymphadenectomy for survival, many recent authors have leaned towards the appropriateness of this treatment for stage II and III disease. The superiority of D_2 resection in terms of survival rate awaits confirmation through randomized trials initiated in Europe[46]. Extended lymphadenectomy is of definite value for staging purposes and may decrease the incidence of local recurrence[47–52]. However, it has been established from the Japanese experience that extended lymphadenectomy does not prevent further tumour spread to the liver and peritoneal surfaces[5–7]. Volpe and colleagues[53] also demonstrated in a case-controlled study that extended lymphadenectomy improves overall and disease-free survival in all patients, but this difference loses statistical significance when survival of patients with T_{3-4} tumours is analysed separately.

The therapeutic advantage of D_2 lymphadenectomy is limited to stages II and IIIA, because the resection line encompasses the N_2 lymph nodes which are free from tumour, thus improving the margin of resection[5,49,50,52,54,55]. Further extension of dissection probably has no impact on survival[56]. Several studies have reported the prognostic significance of the number or percentage of metastatic lymph nodes dissected[52,57,58]. Findings favour the concept of lymph nodes as 'indicators, rather than governors' of survival[59]. Nevertheless, it is important to recognize that 'reasonably' extended lymphadenectomy (D_2) provides more accurate staging[60], is associated with a lower incidence of local recurrence and increases the rate of curative resection[49–52]. Limited (D_1, perigastric lymph nodes only) lymph node dissection results in a resection line which passes through the planes harbouring cancer in approximately half of the patients[3] who can be resected for cure.

One important argument against extended lymphadenectomy is the associated increased morbidity and mortality[46,61]. In the German Gastric Cancer Study of 1992[52], multiple postoperative complications appeared to be the strongest negative prognostic factor. Considerable difference in short-term results was noted between participating teaching hospitals and local hospitals[46,49,52]. The degree of surgical radicalism was directly related, while morbidity and mortality tended to be inversely related, to the number of cases per year per surgeon or hospital. Changes were also reported[62] in the rates of morbidity and mortality after extended lymphadenectomy consistent with a learning curve pattern. Obviously, this kind of surgery should be performed by experienced surgeons in an appropriate facility[63]. Since the morbidity rate rises after extended lymphadenectomy, an interesting approach to customize the extent of dissection was suggested by Maruyama and colleagues[64].

Current experience with adjuvant chemotherapy

Timing of adjuvant chemotherapy

Experimental studies have revealed that changes in residual tumour cell kinetics occur within 24 h of removal of a primary tumour. A week later a measurable increase in tumour size can be observed[65]. Events in wound healing support tumour implantation and growth[66]. The cytotoxic effect on residual tumour after removal of the primary cancer is more pronounced if chemotherapy is given before surgery or on the day of operation. Chemotherapy is least effective when it is administered 7 days after excision of the primary tumour[67]. It appears, therefore, that administration of adjuvant chemotherapy around the time of operation may be the most favourable time for drug delivery; perhaps surgeons should incorporate this knowledge into the design of new treatment strategies.

Intravenous chemotherapy

The treatment approach that has been most widely investigated in resectable gastric cancer is systemic chemotherapy, initiated 4–6 weeks after operation. Meta-analysis of randomized trials conducted in the West has failed to demonstrate a positive impact of systemic chemotherapy on survival[4]. Yet some investigators view surgery plus chemotherapy as a better strategy than resection alone[9,68]. They argue that recently developed multidrug regimens are more active than the chemotherapy used in previous trials. There is no doubt that response rates with these new regimens are higher but, as yet, none of them has proved to be superior to surgery alone in terms of survival in randomized trials.

Some authors have rightly questioned the optimal timing of chemotherapy administration (preoperative *versus* intraoperative or early postoperative *versus* postoperative)[9,68]. Changes in the relationship of surgery and chemotherapy administration may explain the success of the trials conducted in Japan and South Korea[69–72]. Nevertheless, Wils and colleagues[9] showed in phase II trials of new intravenous chemotherapy regimens, including ones with neoadjuvant administration, that most relapses continue to be intra-abdominal (local, liver metastases, peritoneal spread). Rougier and co-workers[73] reviewed the results of trials of neoadjuvant chemotherapy. A downstaging effect and improved resectability have been assumed for both primary irresectable tumours, identified by exploratory laparotomy, and potentially resectable gastric cancer. However, only one randomized study of neoadjuvant chemotherapy substantiates this downstaging effect[72] and long-term results of this study are not yet available. Of note is the fact that some of the new chemotherapy regimens are associated with considerable toxicity. Although less toxic combinations have been suggested, the rates of recurrence remain between 40 and 60 per cent, despite neoadjuvant or 'sandwich' (preoperative plus postoperative) chemotherapy. Only further randomized trials can demonstrate whether or not the potential for an improved response rate and increased resectability with this approach will be translated into increased survival.

Regional adjuvant chemotherapy

The rationale and pharmacokinetics of regional chemotherapy have been extensively evaluated and summarized in a number of publications[74–76]. Basically, all methods of regional chemotherapy are aimed at providing a high cancerocidal concentration of drug(s) within the tumour-bearing area. Response rate is largely dependent on the intensity of tumour exposure to a drug, and time[77]. The choice of drug(s) (cell cycle phase-specific or non-specific) depends on the time of exposure. With every mode of regional chemotherapy, uniform drug distribution and access to the tumour cells is of crucial importance. All modes of regional chemotherapy produce local pharmacokinetic and therapeutic advantages which are confined to the treated area or body compartment to which drug is selectively introduced.

Intraperitoneal chemotherapy. Results of three randomized trials[78–80] have demonstrated that intraperitoneal chemotherapy (IPCT) tends to improve survival compared with surgery alone (*Table 1*). In a fourth randomized trial no difference in survival was noted[81]. Analysis of recurrence pattern in randomized trials shows a statistically significant decrease in the incidence of peritoneal spread; such studies have also demonstrated that IPCT has limited or no influence on the incidence of liver and other metastases.

The effectiveness of IPCT appears to depend on the timing of drug administration. When used at the end of surgery or in the early postoperative period, it is

Table 1 Pattern of recurrent disease and survival in randomized trials of adjuvant intraperitoneal chemotherapy in patients with resectable gastric cancer

Reference	Year	Treatment plan	Peritoneal surfaces (%)	Liver metastases (%)	Other metastases (%)	Survival rate at 3 years (%)	Survival rate at 5 years (%)
Hamazoe *et al.*[78]	1994	Intraoperative heated MMC	39	17	27	83	64
		Surgery only	59	18	9	67	52
Yonemura *et al.*[80]	1995	Intraoperative heated MMC + CDDP	9	5	9	57†	50†
		Surgery only	22	16·7	17	35	28
Yu *et al.*[79]*	1994	Early postoperative MMC on day 1 and 5-FU on days 2–5	4	6	12	66	—
		Surgery only	32·1	5·7	5·7	56	—
Sautner *et al.*[81]	1994	Delayed postoperative CDDP	–	–	–	33	21
		Surgery only	–	–	–	30	23

*Results at 3 years of follow-up. †In patients with T_{3-4} tumours the difference was significant at both 3 and 5 years. MMC, mitomycin C; CDDP, cisplatin; 5-FU, 5-fluorouracil

associated with alteration in the natural history of the disease. Delayed administration has no impact[81]. The time-dependent effectiveness of this therapy would be predicted by the 'tumour cell entrapment' hypothesis[45] and stresses the importance of uniform drug distribution to anatomical sites at high risk of cancer recurrence[82,83]. Dye studies with IPCT show that access of a drug to all peritoneal surfaces is imperfect, even during intraoperative administration when the abdominal wall has been closed. Unless instillation occurs in the early postoperative period, distribution of intraperitoneally administered drugs is further compromised by adhesions and many surfaces remain untreated. A definite trend toward tumour recurrence on these untreated surfaces has been reported[82,84,85]. Limited penetration of intraperitoneally administered drugs[86–89] dictates the necessity for their delivery at the time when surfaces at risk are optimally exposed[90].

Hyperthermic IPCT is also associated with a trend toward improved survival. Experimental studies[91] indicate that the combination of IPCT and hyperthermia increases tumour cell exposure and potentiates the cytotoxicity of chemotherapy; heat alone can cause direct damage to tumour cells. Intraperitoneal chemohyperthermia compared favourably with normothermic IPCT and surgery alone in a randomized trial[80]. While perioperative IPCT is able to decrease the incidence of peritoneal spread after curative resection and tends to improve survival, its impact on lymphatic and haematogenous metastases is limited.

Combination of regional and systemic chemotherapy. Juhl and co-workers[92] have shown, in patients with resectable gastric tumours, that cancer cells can be detected immunocytologically in 25 per cent of bone marrow aspirates; this incidence does not increase with stage. Cancer cells in peritoneal washings are detected in 24 per cent of patients with stage IB and in 40 per cent of those with stage II or III disease. These data correspond to the known incidence of haematogenous and peritoneal metastases reported earlier[10–19]. They build a strong rationale for combining systemic and intraperitoneal chemotherapy in selected groups of patients at risk of systemic cancer dissemination.

In two phase II studies reported recently[93,94] delayed postoperative IPCT was combined with either preoperative or postoperative systemic chemotherapy. These treatments were associated with altered metastatic patterns (decreased incidence of peritoneal spread and liver metastases) and a 3-year survival rate of 50 per cent, considerably better than the widely acknowledged figures. A prospective randomized trial using neoadjuvant systemic chemotherapy with or without postoperative IPCT is currently in progress[95]. The major disadvantage of this treatment strategy is that delayed administration of IPCT is associated with compromised drug distribution in the peritoneal cavity and a high rate of failure of drug access.

Another potentially advantageous strategy utilizing regional chemotherapy was reported by Tansug and coworkers[96]. In this case-controlled study, a 3-day cycle of intraportal chemotherapy and IPCT was started in the early postoperative period followed by five cycles of intravenous chemotherapy. With an average 3-year follow-up, there was a 50 per cent reduction in the incidence of liver metastases and a 60 per cent reduction in the incidence of peritoneal seeding.

Intralymphatic chemotherapy. The abdominal lymph nodes are one of the major sites of gastric cancer metastasis and may be one of the 'key disseminating' sites[20] following surgery. Recent technological advances in targeted drug delivery have provided the opportunity of improved drug access to retroperitoneal lymph nodes, with the help of carriers such as carbon particles and liposomes.

Takahashi and co-workers[97–99] reported their experience with mitomycin C adsorbed on activated carbon particles; this was injected before operation through an endoscope at four points around the tumour or, during surgery, into the subserosal layer of the stomach or intranodally. Examination of resected lymph nodes revealed that carbon particle distribution is dependent on the preservation of lymph flow through a lymph node. Hence, this approach may be effective mainly for small foci or micrometastases in the lymph nodes. A statistically significant improvement in long-term survival was noted with all modes of drug delivery. These researchers also conducted a prospective randomized trial[99], with the same drug and carrier, for prophylaxis of peritoneal dissemination after curative surgery. They demonstrated a statistically significant improvement in survival over surgery alone. Unfortunately, no data regarding the incidence of peritoneal seeding were provided and it may be suggested that carbon particles, being foreign bodies, are rapidly isolated from the free peritoneal cavity and release mitomycin C only at the area where they are deposited. This mode of delivery of chemotherapy may find its best application in prophylaxis of local recurrence resulting from a narrow margin of resection in the gastric bed.

Towards a consolidated management strategy for resectable gastric cancer (*Fig. 1*)

Preoperative staging of gastric cancer has certain well recognized limitations, but it can provide valuable information about histological diagnosis, tumour type, location and macroscopic type of growth. The presence of metastases at extra-abdominal sites and in the liver can be detected with reasonable sensitivity. Surgical exploration, with intraoperative frozen-section examination, is another important method of staging before resection. A major objective of the surgeon is to define the point of diminishing returns in gastric cancer surgery. Selection of the extent of gastric resection, as well as of lymphadenectomy, is of paramount importance and must aim to achieve complete resection of tumour. 'Reasonably' extended lymphadenectomy (D_2) is associated with an increased rate of curative resection, more accurate staging and a decreased rate of local recurrence. With experience, the morbidity associated with this procedure can be within acceptable limits.

It seems feasible to direct intensive adjuvant therapy to 'key disseminating sites'[20] which are actually at risk in a particular patient. Among the decisions that have to be made at operation is an assessment of the risk of intraperitoneal spread after surgery. Diffuse, poorly differentiated, Borrmann type III and IV cancers, as well as any cancer type with serosal surface invasion greater than 2 cm and invasion of adjacent structures, or free intraperitoneal cancer cells, are associated with a high risk of subsequent peritoneal spread[100–103]. For these patients IPCT is a valuable adjuvant which should preferably be used at operation or early in the postoperative period.

Intraoperative findings and thorough histological examination of surgical specimens can provide the information needed for the selection of patients at high risk of systemic spread. A simple and effective prognosticator is the number or percentage of metastatic lymph nodes. Several features, detectable by simple light microscopy (intestinal tumour type, growth pattern, percentage and level of metastatic lymph nodes, lymphatic and venous vessel involvement) and immunohistochemical examination of cell surface antigens, can help to predict the probability of liver metastasis. Because no method of adjuvant treatment has been shown to be equally effective in preventing all variants of gastric cancer spread, the selection of postoperative adjuvant treatment (systemic and/or regional) based on predicted risk of, for example, liver or retroperitoneal lymph node metastasis seems to be a reasonable approach. In this context the role of

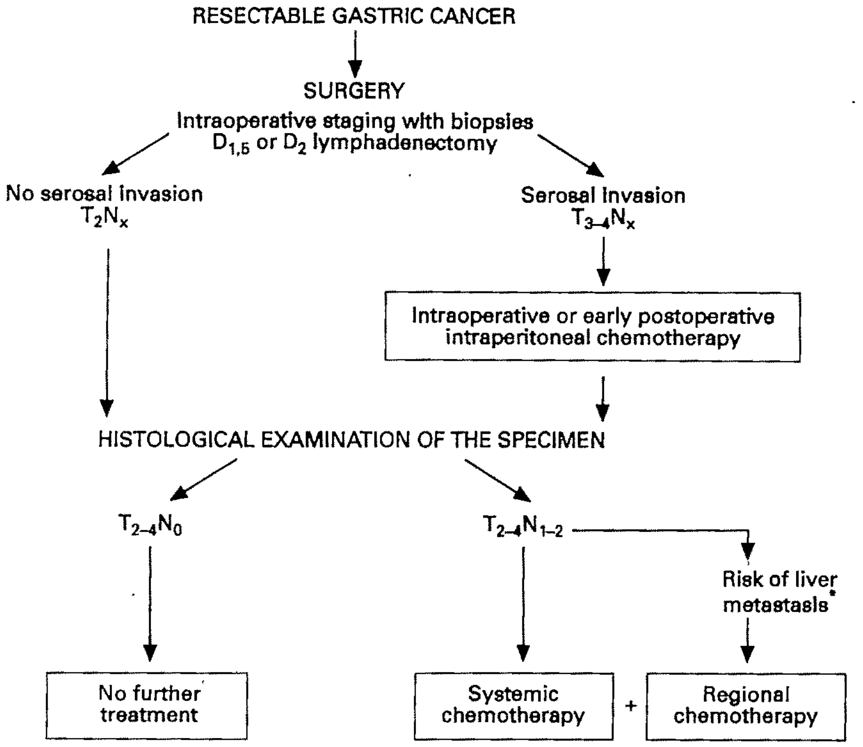
RESECTABLE GASTRIC CANCER
SURGERY
Intraoperative staging with biopsies
$D_{1.5}$ or D_2 lymphadenectomy
No serosal invasion
T_2N_x
Serosal invasion
$T_{3-4}N_x$
Intraoperative or early postoperative intraperitoneal chemotherapy
HISTOLOGICAL EXAMINATION OF THE SPECIMEN
$T_{2-4}N_0$
$T_{2-4}N_{1-2}$
Risk of liver metastasis*
No further treatment
Systemic chemotherapy
+
Regional chemotherapy

Fig. 1 Treatment strategy for resectable gastric cancer. *Patients selected on the basis of blood and lymphatic vessel involvement, cell adhesion molecules associated with liver metastasis, and cancer type

intraoperative intralymphatic or perioperative intraportal and/or intrahepatic chemotherapy deserves further evaluation.

In conclusion, it should be understood that the authors recognize that the suggested concept is rather complicated. Nevertheless, attempts to simplify the approach to treatment, thereby creating a universal treatment modality, are obviously unsuccessful.

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British Journal of Surgery 1996, 83, 734–738

Review

Role of the Shouldice technique in inguinal hernia repair: a systematic review of controlled trials and a meta-analysis

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The Shouldice technique for inguinal hernia repair has been suggested by some authors as the best conventional method against which other methods using prostheses should be compared. The paper which follows is a systematic review involving a comprehensive search of the medical literature to identify all clinical trials (article or abstract) evaluating the Shouldice repair. After assessment of certain quality criteria, the best studies were pooled in a meta-analysis. Nine publications were found with 11 study arms. In ten studies the results of the Shouldice technique were better than the results of the control arm. Six studies could be pooled in a meta-analysis of 2500 patients; Shouldice was significantly better than control methods (relative risk 0·62 (95 per cent confidence interval 0·45–0·85)). In spite of possible bias caused by different variables (modifications in operative technique, suture material, level of surgeon, follow-up methods and outcome measurement), the results of this systematic review suggest that the Shouldice method is the best current conventional technique for inguinal hernia repair.

Inguinal hernia repair is the most frequently performed operation in general surgery[1,2]. Recurrence rates are at least 10–15 per cent in large surveys[2–6] and so improvement of results would have a great medical and economic impact. Recurrence rates vary considerably for the various techniques; the best results are achieved by surgeons reporting personal series using standard methods[7–9]. An increasing number of surgeons in the Netherlands uses the so-called Shouldice technique[4] which has been advocated as the 'gold standard' or, more appropriately, the 'current best conventional method' with which the results of new methods such as laparoscopic techniques should be compared[3]. Recurrence rates of the Shouldice technique coming from specialist centres are as low as 0·6–1·4 per cent[2,3,7,9]. However, under trial conditions in non-specialized centres the recurrence rates for the Shouldice technique vary between 0 and 10 per cent[10–19] and the superiority of this technique is therefore uncertain.

The aim of this study was to assess the results of the Shouldice technique in a systematic review of controlled trials using a meta-analysis if possible.

Method of analysis

Prospective controlled trials addressing Shouldice herniorrhaphy were identified by searching the Medline database for the years 1966–1994 and Embase for the years 1974–1994. The following keywords were used: inguinal hernia and Shouldice. Abstract books of international meetings and recent journals were hand-searched. All studies identified were included (journal articles and abstracts). Authors were contacted when abstracts lacked necessary information.

For each trial included three authors (M.P.S., J.K. and D.v.G.) individually collected information on patient characteristics, comparability of study groups, type of hernia, number of patients, method of randomization, operative technique used, methods of follow-up and outcome measurement. The quality of the trials was assessed using these criteria. The trials were then listed in order of decreasing quality. Differences in surgeon's level of training and the materials used were analysed but not weighed as quality criteria. Differences of quality assessment (about 15 per cent) between the assessors were discussed and full agreement was reached. A maximal score of 9 points was possible when all criteria were positive.

A meta-analysis was performed on randomized trials concerning primary hernia that scored more than 5 points. Relative risk ratios and 95 per cent confidence intervals (c.i.) were used on an individual basis and pooled according to the Mantel–Haenzel method (fixed effects model). Heterogeneity was assessed clinically and statistically. In a sensitivity analysis odds ratios were also calculated according to the Mantel–Haenzel method, as well as the DerSimonian Laird method (random effects model).

Results

Nine studies were traced, six from Medline and three by the hand-search (*Table 1*). Two were in abstract form and the authors were contacted for additional information. Embase yielded no additional studies. One study[19] had four study arms comparing a Bassini technique using two different suture materials (absorbable and non-absorbable) with a standard Shouldice and a modified Shouldice repair; in the latter method two instead of four suture rows were used for repair of the inguinal floor. The Bassini group with the better results was used as control against the standard Shouldice as well as the modified Shouldice group. Another study[18] had four arms comparing the Shouldice technique with two different suture materials (polypropylene and steel) and two control methods (Bassini and McVay). As both control arms had comparable recurrence rates one was used as control for Shouldice with polypropylene sutures and the other as control for Shouldice with steel sutures. Eleven studies could thus be used for analysis.

Paper accepted 8 December 1995

Table 1 Shouldice repair *versus* other techniques

Reference		Year	No. of hernias	Control method	Recurrence rate for control method (%)	Recurrence rate for Shouldice method (%)
Oosterhuis and Greep[13] (Abstract)		1986	263	Bassini–Stetten	6·8	4·8
Hoffmann *et al.*[12]		1991	155	Bassini	10·9	1
Tran *et al.*[14]		1992	128	Bassini–Kirschner	12·5	10
Panos *et al.*[15]		1992	272	McVay	8·8	6·6
Kingsnorth *et al.*[16]		1992	322	Bassini darn	2·3	4·6
Paul *et al.*[17]		1994	244	Bassini	9·6	1·7
Kux *et al.*[11]	I	1994	209	Lichtenstein	0·3	0
Kux *et al.*[19]	IIa	1994	447	Bassini	7·5	2·5
	IIb			Bassini	7·5	1·4*
Fingerhut *et al.*[18] (Abstract)	Ia	1993	1593	Bassini	7	6†
	Ib			McVay	6·8	2·9‡

*Modified Shouldice repair using two rows of sutures. Shouldice repair using †polypropylene or ‡steel sutures

Table 2 Information collected on trials and scoring of quality

Criterion	Quality requirement
1 Comparability of patients	+ Comparable for type of hernia, age, sex, abdominal pressure factors and bilaterality ± Comparable for two or three factors – Comparable for less than two factors
2 Type of hernia	+ Only primary hernia – All types of hernia including recurrent hernia
3 Number of patients	+ More than 200 patients – Less than 200 patients
4 Randomization	+ Randomized. Details given of method of randomization ± Randomized. No details given of method – Non-randomized
5 Operative techniques	+ Well defined, Shouldice by accepted standard, variation in material accepted ± Modified, but complete incision of fascia transversalis and two- or three-layer reconstruction – Unclear
6 Methods of follow-up I	+ Follow-up at least 24 months more than 90 per cent ± Follow-up at least 12 months more than 80 per cent – Not clear or shorter than 12 months
7 Methods of follow-up II	+ More than 90 per cent by physical examination ± More than 80 per cent by physical examination – Less than 80 per cent by physical examination
8 Outcome measurement I	+ Independent surgeon – Operating surgeon or unclear
9 Outcome measurement II	+ Lump in groin, not necessarily reoperated ± Lump in groin and reoperated – Unclear

Table 3 Studies in descending order of quality

	Quality criteria*									Total points†
	1	2	3	4	5	6	7	8	9	
Randomized trials										
Fingerhut *et al.*[18] Ia	+	+	+	+	+	+	+	–	+	8
Fingerhut *et al.*[18] Ib	+	+	+	+	+	+	+	–	+	8
Paul *et al.*[17]	+	+	+	+	+	±	±	–	+	7
Oosterhuis and Greep[13]	±	+	+	±	+	+	+	–	+	7
Panos *et al.*[15]	±	+	+	+	+	±	±	–	±	6
Tran *et al.*[14]	+	+	–	±	+	+	±	–	+	6
Kingsnorth *et al.*[16]	±	–	+	+	+	±	±	–	±	5
Kux *et al.*[11] I	+	+	+	±	±	–	–	–	–	4
Non-randomized trials										
Kux *et al.*[19] IIa	+	+	+	–	+	±	+	–	–	5·5
Kux *et al.*[19] IIb	+	+	+	–	±	±	+	–	–	5
Hoffmann *et al.*[12]	±	–	–	–	+	–	–	–	–	1·5

*See *Table 2.* †Total points were calculated for each trial by assigning 1 point to '+', 0·5 to '±' and 0 to '–'

Table 4 Meta-analysis of randomized trials with scores above 5 points are shown

	Shouldice technique		Control repair		
Reference	No. of patients randomized	No. of recurrences	No. of patients randomized	No. of recurrences	Relative risk
Fingerhut *et al.*[18] Ia	400	24	413	29	0·85 (0·51–1·44)
Fingerhut *et al.*[18] Ib	383	11	397	27	0·42 (0·21–0·84)
Paul *et al.*[17]	119	2	125	12	0·18 (0·04–0·77)
Oosterhuis and Greep[13]	103	5	160	11	0·71 (0·25–1·97)
Panos *et al.*[15]	136	9	136	12	0·75 (0·33–1·72)
Tran *et al.*[14]	65	7	63	9	0·75 (0·30–1·90)
Pooled results	1206	58	1294	100	0·62 (0·45–0·85)*

Values in parentheses are 95 per cent confidence intervals. *$P = 0{\cdot}003$, Mantel–Haenzel test; Epi Info computer program

Table 5 Different pooling methods for the six studies included in the meta-analysis

	Point estimate
Relative risk ratio (Mantel–Haenzel)	0·62 (0·45–0·85)
Odds ratio (Mantel–Haenzel)	0·60 (0·43–0·83)
DerSimonian Laird	0·63 (0·44–0·90)
Breslow–Day test for heterogeneity	$P = 0{\cdot}28$

Values in parentheses are 95 per cent confidence intervals

Studies were analysed according to a series of quality criteria (*Table 2*) and are listed in descending order of quality in *Table 3*. Recurrence rates were lower after Shouldice repair in ten of the 11 studies. In five of the 11 the difference was significant (two of eight randomized studies and all three non-randomized studies). Randomization was considered the key factor in the meta-analysis. The best six studies were considered reasonably homogeneous and suitable for pooling (see Discussion). The results of the meta-analysis are shown in *Table 4*. The relative risk ratio for pooled studies was 0·62 (95 per cent c.i. 0·44–0·87) in favour of the Shouldice technique. When the two lowest scoring trials were included in the pooled results the relative risk was 0·66 (95 per cent c.i. 0·49–0·89), still a significant difference in favour of the Shouldice technique. *Table 5* shows the results when different pooling methods were used; the results are consistent.

Discussion

The differences in recurrence rate after inguinal hernia repair using the Shouldice technique and control methods are small but, because extremely large numbers of these operations are performed each year, the medical and economic consequences of selecting the best method are considerable. However, large series with hundreds of patients and a long follow-up would be required to identify significant differences in outcome in individual trials; this would be a costly and time-consuming business. In the comparative studies of the Shouldice technique reviewed in this article the number of patients included is relatively small. The use of meta-analysis makes pooling of the results possible although it must be recognized that interpretation of pooled data carries a risk. Prospective studies are combined into a retrospective review with unavoidable limitations that are difficult to identify and quantify. In the present meta-analysis patient demographics, type of hernia and bilaterality, prevalence of chronic obstructive pulmonary disease, constipation and prostatism were comparable between groups. Specific factors, however, might cause bias, such as differences in methodology (methods of follow-up and outcome measurement) or in surgery (operative technique, surgeon's expertise and materials).

Follow-up by physical examination within a period of 2–5 years reveals about 50 per cent of the 'final' recurrence rate at 20 years[5,6,21–25]. In the studies included in the meta-analysis, for 516 patients follow-up was complete in 80 per cent for a minimum of 12 months, and for 1984 patients it was complete in 90 per cent for a minimum of 24 months. The mean follow-up was 5 years in the study of Fingerhut *et al.*[18] and 3·5 years in the other studies. In all studies at least 80 per cent of patients were examined by a physician. It is certain that long-term recurrence rates will be higher after complete follow-up, but it is considered unlikely that these small differences in duration of follow-up will influence the outcome of relative risk ratios. It is probable that after 20 years of follow-up the relative risk ratios will remain approximately the same. The definition of the outcome measurement of recurrence was not standard in all studies and varied from 'inguinal tumefaction, tender or not, associated or not with the perception of a hernia sac, detected by the patient or his attending physician and confirmed whenever possible by re-operation'[18] to 'bulge felt at external ring exacerbated by valsalva maneuver and verified by reoperation'[15] or 'necessitating provision of a truss'[14,17]. One study described recurrences as 'failures'[13]. In two studies[13,18] only half of the recurrences had been reoperated at the time of publication. The variation in definition and management of recurrence will certainly influence the recurrence rates in the various studies, but the authors believe that it is unlikely that the relative risk ratios are influenced.

In the six studies included in the meta-analysis, the technique used for Shouldice method was defined according to the guidelines of Glassow[7]. Although surgeons are known to modify techniques to suit personal preference and individual patients[4,26], the techniques in these studies were most probably uniform. It may be assumed that surgeons specializing in hernia surgery probably achieve better results than general surgeons who perform the operation less frequently, although the excellent results reported from specialist centres are mainly based on retrospective analysis[2,7]. There is no evidence from prospective studies that qualified surgeons perform better than surgeons in training; in all but one of the studies[18] in this survey the operations were performed by a combination of non-specialist surgeons and surgeons in training. Better results for the qualified surgeon than the trainee were suggested in one study[16], but the difference was not statistically significant. In other studies with a relevant analysis no difference was found[13,17,27].

Traditionally, many surgeons stress the importance of non-absorbable suture material in hernia repair, although some feel that absorbable sutures which decay slowly may be used successfully[9]. In the present survey Fingerhut *et al.*[18] used steel sutures (trial Ib). Oosterhuis and Greep[13], Hoffmann and colleagues[12] and Kingsnorth *et al.*[16] used absorbable monofilament sutures, and the others used non-absorbable monofilament sutures. Only in one prospective study was this aspect studied specifically and no significant difference in recurrence rate was found when non-absorbable and absorbable material was used[28]. A significant difference in favour of steel suture *versus* polypropylene was found by Fingerhut *et al.*[18], both are non-absorbable. However, in a recent report after a follow-up of more than 5 years this difference was smaller than that described originally and was not statistically significant[20]. In five of six studies included in the meta-analysis non-absorbable suture material was used and leaving the Oosterhuis study out of the pooling did not influence the results. The Shouldice Hospital surgeons, having favoured steel for many years, agree that monofilament non-absorbable material can be used instead.

The difference in recurrence rates after hernia repair using the Shouldice technique between the studies reviewed by the present authors and retrospective reports by Shouldice experts[2] may be explained by difference in quality of method of follow-up, different level of surgical experience, differences in definition and measurement of outcome, and study design (prospective *versus* retrospective). In the present survey it appears that the Shouldice technique leads to better results than the other operations, which usually amounted to the preferred technique in the individual institution concerned, before the start of the hernia study. Equal expertise in both techniques is required before a patient can properly be included in a prospective randomized trial. However, it is likely that surgeons were less experienced in the new technique (Shouldice) in most of the above studies and that even better results could have been achieved with more experience of the Shouldice method.

Whether publication bias influences this analysis is a moot point. Theoretically, unpublished studies may have yielded negative results after Shouldice repair, but it is doubtful that investigators who have put a large amount of energy into a prospective trial would abstain from publishing simply because of a negative outcome. However, the lack of willingness on the part of medical journals to publish negative results is a cause for statistical concern.

In performing this meta-analysis risks have been taken. The numbers used are relatively small and an explanation for the differences in recurrence rate must be found within the above-mentioned variables (possible differences in operative technique, level of surgeon, suture material, follow-up method and duration, and outcome measurement). In spite of these caveats it is concluded from this review and meta-analysis that the Shouldice technique is superior to other conventional methods. Shouldice herniorrhaphy is probably the best conventional method of hernia repair; the success or otherwise of laparoscopic repair and other methods, such as the Lichtenstein[8] technique, should be measured against this standard.

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British Journal of Surgery 1996, 83, 739–749

Review

Colorectal cell kinetics

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The assessment of cell proliferation in colorectal tissue may provide information with both prognostic and therapeutic implications. A variety of methods are available, including flow cytometric estimations of S phase fraction, immunohistochemical and autoradiographic visualization of exogenous and endogenous proliferation proteins, and morphological and stathmokinetic techniques. There is some correlation between Dukes stage and proliferation state features, and there is increased proliferative activity throughout the adenoma–carcinoma sequence. Data on cell proliferation rates are difficult to obtain. When correctly applied, the metaphase arrest technique remains the 'gold standard' of measuring proliferation, but its usefulness in clinical practice is limited. Recent studies have employed dual measurement flow cytometry and double labelling techniques to produce rate data.

Adenocarcinoma of the colorectum is the second most common cancer in developed countries[1,2]. It is responsible for 13 per cent of all cancer-related deaths in the USA, a figure mirrored within the UK where Northern Ireland has one of the highest incidences and mortality rates[3–5]. Furthermore, there is evidence that, in geographical areas of high risk, the incidence of colorectal cancer has been increasing over the past 50 years[1,6,7].

For many years, colorectal cancer has been staged according to the criteria set out by Dukes[8] with minor modifications[9–11]. New systems of staging and grading have been introduced[12–14], but none have improved on the high prognostic power of Dukes' classification[15]. However, even Dukes' classification cannot perfectly predict outcome for a particular individual. Factors influencing the final outcome of patients with this condition may lie beyond the scope of macroscopic or histological examination, at the genetic level, where alterations in oncogenes and tumour suppressor genes may result in changes in cell proliferation kinetics.

The cell cycle and cell proliferation

The concept of the cell cycle was first proposed by Howard and Pelc in 1951[16]. It is defined as the period between the midpoint of mitosis and the midpoint of the subsequent mitosis[17]. Within each cycle, replication of cellular DNA occurs during the synthetic or S phase. This is preceded by a period in which it was formerly thought that the cell was at rest, the first gap or G_1 phase. After DNA synthesis the cell proceeds towards the mitotic or M phase by way of a further period of apparent inactivity, designated the second gap phase or G_2[17].

Cells within any living tissue may be divided into three kinetically distinct categories[18]. One group contains actively proliferating cells which are passing through the various phases of the cycle. The second population consists of cells which have left the cycle, have differentiated and are destined to die without further division. The third population comprises cells which have left the cycle temporarily and remain in a resting state (G_0) ready to rejoin the dividing population following a suitable environmental stimulus[19].

The growth of any normal or abnormal tissue is a dynamic process dependent on the balance between cell production, cell death and growth arrest[20]. The rate of cell production is controlled by the proportion of cells which are cycling, known as the growth or proliferative fraction[21], and the length of the cell cycle. Thus a greater number of cycling cells and/or a shorter cell cycle time will result in increased cell production. Counterbalancing this increase is the rate of cell loss by exfoliation, cell death or migration to other tissues[20]. In the adult, synthesis and degradation are balanced to maintain a steady state[22,23] except in areas of abnormal growth, such as cancer. Growth in tumours is, therefore, dependent on an increase in the proliferative compartment and/or alterations in the length of the cell cycle and/or a decrease in the extent of cell loss[24].

Interest has surrounded the investigation of the proliferative fraction of tumours for three reasons. First, cell proliferation characteristics may reflect the aggressiveness of a tumour and its eventual prognosis[25–28]. Second, rapidly proliferating tumours may be more radiosensitive; patients with such a malignancy may benefit from a regimen of accelerated fractionation radiotherapy to counter the significant repopulation that is possible during conventional fractionated radiotherapy[29,30]. Finally, colorectal cellular proliferation has been the subject of considerable investigation over the past 15 years because of the high and possibly increasing incidence of colorectal cancer, together with the unreliable nature of prognostic information. This review summarizes present knowledge of colorectal cell kinetics.

DNA ploidy and S phase fraction

The majority of normal human somatic cells within the proliferative compartment of the cell cycle will be in G_1 and will contain 46 chromosomes (23 pairs), the normal

Paper accepted 17 January 1996

diploid karyotype. During S phase the DNA content gradually increases to attain the tetraploid state immediately before division (G_2 + M). The capability of certain fluorescent dyes to bind with DNA[31] allows assessment of the DNA content in large numbers of individual cell nuclei by flow cytometry[32–34]. The proportion of cells in various phases of the cell cycle can be quantified. Furthermore, the development of disaggregation techniques which made possible the analysis of archival material from formalin-fixed paraffin-embedded histological samples[35,36] has prompted many retrospective investigations.

Flow cytometric analysis of human tumour cell suspensions has been used extensively to determine the fraction of cells in the G_1, S and G_2 + M phases of the cell cycle[37–40]. The proportions of cells in the S phase (S phase fraction) or in the S and G_2 + M phases combined (proliferative fraction) are considered to be a measure of the relative size of the proliferating cell population. Many studies also report the DNA index of the cell population along with phase fraction data. The DNA index is defined as the ratio of the peak of the relative DNA content of the G_1 cells of the test sample population divided by the peak of the relative DNA content of diploid G_1 reference cells[41]. Cells with a normal diploid karyotype have, by definition, a DNA index of 1·0. Cell populations in which there are two or more distinct G_1 populations are said to show DNA aneuploidy. Therefore, tumours which have cell populations whose G_1 peak can be discriminated from the diploid G_1 are designated as DNA aneuploid[41].

Flow cytometry does, however, have a number of disadvantages. Obtaining single cells from solid tumours, either fresh or in fixed material, requires enzymatic or mechanical disaggregation. These methods produce single cell or nuclei suspensions containing not only the epithelial population of interest but also a variable quantity of non-malignant stromal cells. The loss of histological information makes it difficult to ensure that the suspension is cytokinetically representative of the tumour. Furthermore, the more harsh disaggregation techniques required for the extraction of cells from archival material can result in excess debris, making analysis impossible[42].

Assessment of the S phase fraction has two main problems. First, definition of the exact size of the S phase is difficult as it overlaps the G_1 and G_2 + M phases of the DNA histogram[43,44]. In addition, as the S phase fraction is often small (less than 10 per cent) any error in its calculation can result in incorrect placement of the tumour into a slowly or rapidly proliferating category[45]. Both these problems are compounded by the presence of an overlapping DNA aneuploid population[46]. A further complicating factor is that colorectal tumours have been demonstrated to be heterogeneous with regard to their ploidy status, S phase fraction and proliferative fraction[47–49]. Results obtained for these parameters differ not only between central (often necrotic) and peripheral areas of the tumour, but also between superficial and deep portions[50,51]. No consensus has been reached as to how tumours should be represented or to the importance of samples from central areas compared with those from the advancing tumour edge.

An association between DNA ploidy of colorectal adenocarcinomas and prognosis was first reported by

Table 1 Literature review of flow cytometric DNA content of colorectal carcinomas

						Correlation with				
Reference	Year	No. of cases studied	Site	Method	Aneuploid (%)	Survival	Recurrence	Dukes stage	Grade	Site
Armitage *et al.*[53]	1985	134	C/R	PE	54	+	n.i.	—	—	n.i.
Baretton *et al.*[49]	1991	163	C/R	PE	60	+	+	—	—	+
Bosari *et al.*[54]	1993	173	C/R	PE	58	—	n.i.	—	n.i.	+
Cavaliere *et al.*[55]	1994	105	C/R	F	56	—	n.i.	+	n.i.	n.i.
Costa *et al.*[56]	1992	110	C/R	F	66	—	n.i.	—	—	+
Deans *et al.*[57]	1993	275	C/R	PE	47	—	n.i.	—	—	n.i.
Enker *et al.*[58]	1991	176	C/R	F	64	—	—	—	—	—
Fausel *et al.*[59]	1990	27	C/R	PE	56	+	n.i.	+	n.i.	n.i.
Giaretti *et al.*[60]	1991	115	C/R	F/PE	62	+	n.i.	—	—	n.i.
Goh *et al.*[61]	1987	203	R	PE	64	+	n.i.	n.i.	—	n.i.
Heimann *et al.*[62]	1992	52	C/R	PE	60	+	n.i.	+	—	—
Hiddemann *et al.*[63]	1986	88	C/R	F	82	n.i.	n.i.	—	+	n.i.
Jones *et al.*[64]	1988	119	C/R	PE	67	+	n.i.	+	—	—
Kouri[65]	1993	205	C/R	F	62	n.i.	n.i.	—	n.i.	—
Lanza *et al.*[66]	1994	123	C/R	F	73	n.i.	n.i.	—	—	+
Lindmark *et al.*[48]	1991	123	C/R	F	63	n.i.	n.i.	—	—	+
Meling *et al.*[67]	1991	406	C/R	F	61	n.i.	n.i.	+	—	n.i.
Quirke *et al.*[68]	1987	125	R	PE	54	+	n.i.	—	—	n.i.
Quirke *et al.*[47]	1985	50	C/R	F	72	n.i.	n.i.	—	—	n.i.
Rognum *et al.*[69]	1982	100	C/R	F	63	—	n.i.	—	—	n.i.
Schillaci *et al.*[70]	1990	70	C/R	F	76	+	—	+	—	—
Schutte *et al.*[71]	1987	279	C/R	PE	62	—	n.i.	—	—	n.i.
Scott *et al.*[72]	1987	121	R	PE	50	+	+	+	—	n.i.
Silvestrini *et al.*[73]	1993	181	C/R	F	63	—	—	+	—	—
Stipa *et al.*[74]	1993	55	C/R	F	71	—	n.i.	+	—	n.i.
Tomoda *et al.*[75]	1993	100	C/R	F	59	—	+	—	—	—
Wolley *et al.*[52]	1982	33	C	F	39	+	n.i.	—	—	n.i.

C, colonic tumours; R, rectal tumours; F, fresh or frozen tissue; PE, paraffin-embedded tissue; —, no statistical correlation; +, statistically significant correlation; n.i., not investigated

Wolley *et al.*[52], who showed that patients with DNA aneuploid tumours had a worse clinical outcome with early recurrence and death. Since then a large volume of data has been produced, much of which is contradictory. The overall incidence of DNA aneuploidy in colorectal carcinomas is 39–82 per cent (*Table 1*). Some studies have found increasing DNA aneuploidy to be associated with more advanced tumours. Others have limited this correlation to Dukes B[64] or C[62] tumours alone. This finding is understandable because nearly all Dukes A tumours have favourable outcome while, conversely, most Dukes 'D' tumours have a poor prognosis. Some studies have found no correlation between DNA ploidy and stage or histological grade (*Table 1*), or any other histopathological parameter[66,73].

Several studies have demonstrated a high incidence of DNA aneuploidy in tumours that recurred early (*Table 1*). Many support Wolley's original conclusion that DNA aneuploidy is associated with a poorer prognosis, some state that it is an independent prognostic variable in a logistic regression analysis[53], a finding that others fail to corroborate[58,61,64,70,74,75]. Some authors, who failed to note any correlation between DNA aneuploidy and clinicopathological features, have found an association between multiploid tumours (those having more than one DNA aneuploid population) and unfavourable patterns of growth[66], male patients[56], advanced stage of disease and decreased 5-year disease-free survival (*Table 2*).

Adenomas have a much lower incidence of DNA aneuploidy than carcinomas[76]. DNA aneuploidy is, however, more common in large adenomas[76,77] or adenomas with severe dysplasia[77]. An increased rate of DNA aneuploidy is also seen in the adenomas of patients with a positive family history of colorectal carcinoma[78] or in the mucosa of patients with ulcerative colitis who are at increased risk of developing cancer[77].

Reported S phase fraction in colorectal tumours ranges from 0 to 75 per cent (*Table 3*). No correlation with age, sex, tumour site, grade or prognosis has been noted, but an association between higher S phase fractions and more advanced tumour stage has been reported (*Table 3*). An association between high S phase fraction and DNA aneuploid tumours has been noted by some[54,58] but not all investigators[48]. The proliferative fraction has been correlated with Dukes stage by some[58] but not others[68]. There are conflicting reports as to the correlation between the proliferative fraction and prognosis[68].

While flow cytometry has the capacity to analyse very large numbers of cells quickly, the cost of the equipment often confines its use to specialist centres. Many simpler methods can be used to assess proliferation.

Mitotic index

The calculation of a mitotic index for tumours as a method of assessing cell proliferation uses identification of the only phase of the cell cycle that can be recognized by simple histological examination. Several methodological problems exist. Mitotic cells form only a small quantity of the total number of cells present in any sample of colorectal tissue. Thus a large number of cells (more than 3000) must be counted if an accurate index is to be calculated. Recognition of mitoses can be difficult, and fragmented or pyknotic nuclei and other suspicious cells may be included in the count if careful examination is not

Table 2 Literature review of flow cytometric multiploid DNA content of colorectal carcinomas

						Correlation with				
Reference	Year	No. of cases studied	Site	Method	Multiploid (%)	Survival	Recurrence	Dukes stage	Grade	Site
Cavaliere *et al.*[55]	1994	105	C/R	F	15	+	+	n.i.	n.i.	n.i.
Costa *et al.*[56]	1992	110	C/R	F	13	n.i.	n.i.	+	—	—
Hiddemann *et al.*[63]	1986	88	C/R	F	33	n.i.	n.i.	—	n.i.	n.i.
Lanza *et al.*[66]	1994	123	C/R	F	16	n.i.	n.i.	+	—	n.i.
Schillaci *et al.*[70]	1990	70	C/R	F	49	—	n.i.	—	n.i.	n.i.
Silvestrini *et al.*[73]	1993	181	C/R	F	12–17	+	+	n.i.	n.i.	n.i.

C, colonic tumours; R, rectal tumours; F, fresh or frozen tissue; —, no statistical correlation; +, statistically significant correlation; n.i., not investigated

Table 3 Literature review of flow cytometric S phase fraction of colorectal carcinomas

						Correlation with				
Reference	Year	No. of cases studied	Site	Method	S phase fraction (%)*	Survival	Recurrence	Dukes stage	Grade	Site
Bosari *et al.*[54]	1993	173	C/R	PE	17	—	—	—	n.i.	n.i.
Cavaliere *et al.*[55]	1994	105	C/R	F	Diploid 1–36 Aneuploid 1–47	—	n.i.	+	n.i.	n.i.
Deans *et al.*[57]	1993	275	C/R	PE	17	—	n.i.	n.i.	n.i.	n.i.
Enker *et al.*[58]	1991	176	C/R	F	0–75	—	n.i.	+	n.i.	n.i.
Lindmark *et al.*[48]	1991	123	C/R	F	Diploid 7–31 Aneuploid 8–20	n.i.	n.i.	—	—	—
Hiddemann *et al.*[63]	1986	88	C/R	F	Diploid 14 Aneuploid 25	n.i.	n.i.	n.i.	n.i.	n.i.

*Mean or range. C, colonic tumours; R, rectal tumours; F, fresh or frozen tissue; PE, paraffin-embedded tissue; —, no statistical correlation; +, statistically significant correlation; n.i., not investigated undertaken. Delays in fixation, inevitable in large tumours, may allow mitoses to proceed to completion with few, if any, new mitoses occurring. This may lead to underestimation of the true index[79]. While mitotic counts have been shown to be useful in the prognosis of breast cancer[80] only a few studies have examined the mitotic indices of colorectal tumours[81]; none has related this measurement to prognosis.

Thymidine analogues

Thymidine analogues such as tritiated thymidine ($[^{3}\mathrm{H}]$TdR) and 5-bromo-2′-deoxyuridine (BrdU) can be used as markers of cell proliferation. When present in the correct concentration, these will be incorporated into replicating DNA during the S phase of the cell cycle. Incorporated analogues are detected autoradiographically ($[^{3}\mathrm{H}]$TdR) or immunohistologically (BrdU). Division of the number of cells thus labelled by the total number of cells produces a labelling index (LI), which is a measure of the state of cell proliferation. Use of these analogues to calculate a LI has a significant advantage over the mitotic index in that the S phase of the cell cycle is considerably longer in duration than the mitotic phase in most tissues. The LI is proportionally greater than the mitotic index, thereby producing an index of greater reliability for statistical analysis. However, counting up to 3000 cells to calculate a LI remains time consuming and tedious.

These analogues have been administered both *in vitro* and *in vivo* but both methods can lead to uneven distribution of label. *In vitro* infiltration of tumour fragments may produce unequal diffusion of exogenous analogues to areas of the fragment[82,83]. This is also true of *in vivo* studies because vasculature will influence the amount of label available for uptake to cells in different areas[84]. It has been suggested that tumour cells have a large pool of endogenous nucleotides which cannot be flooded by a single injection or exposure to $[^{3}\mathrm{H}]$TdR or other analogues[85]. All these caveats contribute to LI heterogeneity. To overcome this problem, some investigators may concentrate on highly labelled areas[82,86], but this may lead to erroneously high LIs being reported[82].

$[^{3}\mathrm{H}]$TdR has been used to assess the kinetics of both normal and abnormal colorectal epithelium[87–89]. Studies are mainly *in vitro* because of the ethical problems with the administration of radioactive label to humans. Cell proliferation in the colonic mucosa was thought to be restricted to the lower two-thirds of the crypts[90]. In 1963, two studies demonstrated an extension of the proliferative compartment towards the luminal surface (a so-called stage I defect) in the histologically normal mucosa of patients with familial adenomatous polyposis[91,92]. The phenomenon of an increased proliferative compartment was also recognized in patients with ulcerative colitis or a history of colorectal cancer and in the asymptomatic relatives of patients with familial adenomatous polyposis[93]. Stage I defects have also been demonstrated in adenomas[94,95], the flat mucosa of patients with familial adenomatous polyposis[96,97] and the mucosa of patients with familial colon cancer without polyposis[97,98]. However, the appearance of stage I defects in the rectal biopsies of 75 per cent of asymptomatic controls led to the suggestion that this alteration was a mild deviation from the normal pattern, merely representative of the changing proliferation pattern of an ageing population[99].

Thymidine labelling *in vitro* was also used to demonstrate a further alteration in the pattern of mucosal proliferation in patients who had a previous history of colorectal neoplasm. In these patients the region of DNA synthesis was no longer confined to the lower thirds of the crypt, but had shifted upwards into the middle and upper two-thirds (a stage II defect)[100]. This abnormality was not seen in normal controls[99]. In a study of patients at high risk of developing colorectal cancer, only 30 per cent of biopsies showed a normal pattern of proliferation. Of patients who had a stage I abnormality, 30–60 per cent (depending on the risk group) had an additional stage II defect[93]. The stage II defect is seen less frequently and may represent a slowly evolving loss of regulatory control. Indeed, patients who have had a carcinoma resected and whose colonic mucosa continues to express this defect are at greater risk of developing further adenomas progressing to carcinoma[101].

In vitro thymidine labelling studies on colorectal tumours have reported mean LIs ranging from 0 to 50 per cent (*Table 4*). Slight differences in methodology may partly account for this wide variation. However, in addition to this disparity, several studies have produced directly conflicting kinetic information. Meyer and Prioleau[103] reported that the mean $[^{3}\mathrm{H}]$TdR LI of 90 *in vitro* infiltrated colorectal cancers was 17·8 per cent. They could not identify a significant correlation between the LI and any clinical or morphological feature (*Table 4*). The mean LI in the 55 specimens of histologically normal mucosa examined was 17·2 (range 2·1–40·6) per cent, similar to that of the malignant tissue. However, the LI of the normal mucosa did not correlate directly with that of the carcinoma from the same patient[103]. Trotter *et al.*[25], on the other hand, noted a significantly higher LI for Dukes

Table 4 Literature review of tritiated thymidine labelling indices of colorectal carcinomas

					Correlation with				
Reference	Year	No. of cases studied	Site	LI*	Survival	Recurrence	Dukes stage	Grade	Site
Bleiberg and Galand[97]	1976	7	C/R	24–50	n.i.	n.i.	n.i.	n.i.	n.i.
Costa *et al.*[56]	1992	110	C/R	4–44	n.i.	n.i.	—	—	—
Lieb and Lisco[102]	1966	5	C	3–47	n.i.	n.i.	n.i.	n.i.	n.i.
Meyer and Prioleau[103]	1981	90	C/R	2–40	—	—	—	—	—
Ponz de Leon *et al.*[104]	1991	150	C/R	4–41	n.i.	n.i.	n.i.	n.i.	n.i.
Trotter *et al.*[25]	1985	28	C/R	0–24	n.i.	n.i.	+	n.i.	n.i.
Wolberg and Ansfield[105]	1971	134	C/R	3	n.i.	n.i.	n.i.	n.i.	n.i.

*Median or range. LI, labelling index; C, colonic tumours; R, rectal tumours; —, no statistical correlation; +, statistically significant correlation; n.i., not investigated

A and B tumours (10·1–23·6 per cent) than for Dukes C and 'D' growths (0·1–13·6 per cent) in cultured tumour cells.

BrdU also has been used to assess the state of proliferation[106]. DNA substituted by BrdU can be detected by monoclonal antibodies[106,107] of the type developed by Gratzner in 1982[108]. Labelled cells may then be identified by standard immunohistochemical techniques, which can be quantitated flow cytometrically by the intensity of fluorescence or by assays that measure the optical density of an appropriate chromogen[109,110]. Although yielding similar proliferative data[111], BrdU has a number of advantages over $[^3H]$TdR. It is not radioactive and can therefore be handled safely in the laboratory[112] and administered to patients[28,30,84,110,113–117]. BrdU immunohistochemistry is quicker to perform than autoradiography[109,112,118] and, because BrdU is identified by deposition of a reaction product at the site of the DNA, a clear distinction between positive and negative cells[109,112,119] and improved cytological detail are possible[112].

The detection of BrdU-substituted DNA by monoclonal antibody is dependent on DNA being in the single stranded configuration and thus DNA must be denatured[120,121], a process most commonly performed by exposure to hydrochloric acid[122]. This step may be difficult to control[123], with some authors reporting that the LI is dependent on the concentration of acid to which cells are exposed, the optimal concentration being tumour specific[122].

Using BrdU immunohistochemistry, the LI of normal colorectal mucosa has been reported as 1·9–20·0 per cent[84,117,124,125], of adenomas as 8·0–27·3 per cent[124] and of carcinomas as 16·8–30·8 per cent[117,124]. The biological progression from normal mucosa to carcinoma is characterized by alterations in proliferative activity, significant differences being noted between the LI of normal mucosa and adenomas[124,126], normal mucosa and carcinoma[117], adenoma and carcinoma[126] and even between low-grade dysplasia adenomas and high-grade dysplasia adenomas[124]. In spite of this, no correlation has been noted between the BrdU LI and any clinical or morphological feature of colorectal carcinomas[117].

The changes that occur in histologically normal mucosa as a possible forerunner to the development of neoplasia have also been studied with BrdU. An increase in the BrdU LI and an upward shift in the proliferative compartment (stage II defect) has been demonstrated in the flat mucosa of patients with a colorectal neoplasm[127,128]. Stage II defects have been noted also in background mucosa in adenomas and carcinomas[124], being more pronounced in patients who have a high-grade dysplasia adenoma or an adenoma in association with a carcinoma[128]. However, proliferative activity in normal mucosa immediately adjacent to the advancing edge of a tumour appears to be reduced[125].

To overcome the problems associated with the administration of DNA precursors to assess DNA synthesis directly, proliferation can be assessed by the detection of endogenous proteins or other antigens associated with the cell cycle or its DNA replication mechanism.

Ki-67

The production of Ki-67, a monoclonal antibody that recognizes a nuclear antigen associated with the cell cycle, has permitted further assessment of the state of cell proliferation in various tissues[129]. In continuously cycling cells, the antigen is expressed in all phases of the cell cycle, but cells entering the cell cycle from G_0 do not express the antigen in G_0 or early G_1[130]. Thus Ki-67 expression provides a direct measure of the growth fraction of the tissue[26]. The usefulness of Ki-67 as a proliferative marker was hindered by the sensitivity of the antigen to fixatives and, therefore, the need to use fresh or snap-frozen material for analysis. Furthermore, some have suggested, despite storage at low temperatures, that the antigen may deteriorate with time[131], although this has been disputed[132]. In 1992, two new antibodies to the Ki-67 protein were developed, known as MIB-1 and MIB-3[133]. These were shown to be equivalent to Ki-67 and had the advantage of being able to detect the antigen in formalin-fixed paraffin-embedded tissue after a period of microwave irradiation of the sections. Although these monoclonal antibodies detect an endogenous antigen, heterogeneous staining presents an additional difficulty requiring the counting of a considerable number of cells from each sample to minimize variation[132,134].

A wide range of Ki-67 LI (1–80 per cent) has been reported for adenocarcinomas[135–138]. Many studies have failed to show any correlation between Ki-67 LIs and patient age, lymph node status, tumour size, site, degree of differentiation or Dukes stage[135–140]. However Kubota *et al.*[141] have reported a higher Ki-67 LI in Dukes A tumours, the reverse being noted by Suzuki and colleagues[142] who demonstrated the Ki-67 LI to be significantly greater in Dukes B, C and 'D' tumours than in Dukes A lesions. Others have noted an inverse relationship between the degree of differentiation of the tumour and Ki-67 LI[143].

The Ki-67 LI of normal colonic mucosa is in general lower than that of adenocarcinomas[135,139,144], but no difference has been noted in the LI of mucosa adjacent to tumour and that of mucosa distant from the tumour edge[139]. However, a progressively increasing LI has been noted along the adenoma–carcinoma sequence, with low-grade dysplasia adenomas having a lower index than high-grade adenomas which, in turn, have a lower LI than advanced carcinomas[143,144]. Early cancers have a LI in the same range as that of low-grade dysplasia adenomas, an observation which has been attributed to changes in the submucosal vascular network due to tumour invasion[144].

Considerable correlation has been noted between the LI obtained using Ki-67 and that obtained using other proliferative markers in benign, premalignant and malignant colorectal tissue. These markers include DNA polymerase-α[144], proliferating cell nuclear antigen (PCNA)[144,145], argyrophilic proteins associated with silver staining nucleolar organizing regions (AgNORs)[144] and BrdU[146]. There is also a correlation between the Ki-67 LI and flow cytometrically-derived proliferative fractions[139,147].

Proliferating cell nuclear antigen

PCNA is the 36-kDa non-histone nuclear protein[148] identified as the auxiliary protein of DNA polymerase-δ[149]. Its expression is associated with the S phase of the cell cycle[150], with maximal concentrations seen in the late G_1 and S phases[151,152]. There are three commonly used antibodies (PC-10, 19A2 and 19F4) and, although they all react with similar epitopes[153], they identify cells from different phases of the cell cycle depending on the fixation and immunohistochemical detection techniques used[154–156].

As with other endogenous proliferation markers, PCNA LIs do not permit the measurement of the rate at which cells progress through S phase[157]. The PCNA LI has been correlated with flow cytometrically-derived S phase fraction, but it consistently exceeds it in a series of diverse tumours[158]. Similarly, the PCNA LI is often greater than the LI obtained using other markers in various animal and human tissues[126,144,159]. High PCNA LIs can be seen in normal mucosa of patients with carcinomas[145]. However, stage II defect is not demonstrated by PCNA labelling[126,160], suggesting that it is not as sensitive a marker of predisposition to colorectal cancer. As with BrdU, Ki-67 and other markers, there is a progressive increase in the PCNA LI throughout the spectrum from normal mucosa to adenoma to carcinoma[126,144]. The lower levels of proliferation in early adenocarcinoma shown by other markers have also been demonstrated by PCNA[144].

Teixeira *et al.*[161] demonstrated a correlation between a high PCNA LI and certain features of tumour aggressiveness, including venous invasion, poor differentiation, lymph node involvement and liver metastases. Others have been unable to show a correlation between the PCNA LI and any histological feature[140]. The PCNA LI of carcinomas has been noted to correlate with survival[160,162]. However, there is no association between PCNA proliferating indices and Dukes stage[160].

Other markers of proliferation

Other proliferative markers, including DNA polymerase-α and AgNORs, have been investigated in colorectal tissue. DNA polymerase-α is a component of the DNA replication mechanism which is transcriptionally regulated in a cell cycle-dependent fashion[163] and can be detected using monoclonal antibodies[164,165]. Nucleolar organizing regions are loops of DNA associated with argyrophilic proteins, demonstrable by silver staining. The nucleic acid component comprises the genes for ribosomal RNA (rRNA), so AgNORs act as a marker of rRNA transcription. Counting AgNORs produces data which are now known to be correlated with cell proliferation[79]. Only a few studies have been performed using either of these markers in colorectal tissue[106,144].

Rates *versus* states

The methods for assessing cell proliferation presented so far are cytostatic, only providing an estimate of the fraction of cells in a particular phase of the cell cycle at any given moment i.e. the *state* of proliferation. This information can be misleading as it uses no measure of time. For example, in a population where the cell cycle is long, many cells will appear to be in cycle at a given instant. Hence the LI may be high even though the population is cycling slowly. By including temporal information, useful data on the *rate* of cellular proliferation may be obtained. Collection of such data requires calculation of both the number of cycling cells and the length of their cycle. It is often difficult to obtain complete and accurate quantitation of the two variables on one cell population.

Data on proliferation rates may be expressed in a number of ways, such as the length of the S phase (Ts), the cell cycle time (Tc) or the potential doubling time (Tpot). The Tpot of a cell population estimates the time taken for that population to double in number, taking into account dividing and non-dividing cells but excluding cell loss[166]. Although tumour Tpots are theoretical, they remain the most reliable predictors of the doubling time of clonogenic cells[29]. This information can be used to identify tumours that are capable of a rapid compensatory proliferation in response to adjuvant therapy[29,167,168] and may, therefore, facilitate the selection of more appropriate treatment schedules for individual patients[167].

Tumour size

Although not a direct measure of cell proliferation, early kinetic data on colorectal cancer came from growth rate studies in which the increase in size of either the primary tumour or its metastases was observed by serial radiography. There are five studies of note in which the growth rate of primary tumours was assessed[169–173]. The number of observations made in each case was often small and widely differing doubling times (ranging from 53 to 2355 days) were reported. A radiographic study on the growth of lung metastases suggested that they were generally faster growing than primary tumours, with a mean doubling time of 95 days[166].

Fraction labelled mitosis

In this technique, first described in 1959[174], the cells of interest are pulse labelled using [^{3}H]TdR and the fraction of labelled mitoses determined in samples taken at frequent intervals thereafter. Plotted against time these data generate a curve. The passage of labelled cells that were initially in S phase through the short mitotic phase leads to waves of labelled mitoses. By measuring the width of the waves Ts can be calculated and by measuring the separation of the waves Tc can be determined. Despite the fact that BrdU could now be used as a pulse label, the ethical problem of taking multiple biopsies from patients has severely limited the application of this technique. In investigations that have been performed on colorectal tissue in humans[89,175,176], the Tc of both tumour and mucosa were similar (24–48 h).

Stathmokinetic technique

Stathmokinetic techniques employ agents, such as vincristine and colcemid, which cause arrest and accumulation of proliferative cells in the metaphase stage of mitosis. The method relies on measurement of the slope of the line that describes the accumulation of arrested metaphases over time. The rate of cell production is equivalent to the rate of accumulation of arrested metaphases[177]. To ensure the accuracy of the data it is imperative to establish linearity of metaphase collection, to optimize the dosage of the stathmokinetic agent and to analyse the data correctly[178]. Again the need for multiple biopsies has severely limited the usefulness of this technique in clinical practice. Studies suggest that the Tpot of normal mucosa is considerably shorter than that of colorectal carcinoma[177].

Dual measurement flow cytometry

Following the development of antibodies that recognized BrdU-substituted DNA[18], flow cytometric methods were devised to measure simultaneously the uptake of BrdU and the total DNA content[120]. The monoclonal antibody bound to BrdU can be detected by a fluorescein isothiocyanate-conjugated antibody, which fluoresces green during laser excitation. As anti-BrdU antibodies bind stoichiometrically to BrdU in single stranded DNA, the intensity of green fluorescence is proportional to the amount of BrdU incorporated[120,155]. Simultaneous excitation of intercalated PI (propidium iodide) produces red fluorescence proportional to the double stranded DNA content. The flow cytometric measurements are arranged to form bivariate distributions of DNA content *versus* BrdU content. This enables resolution of the cell cycle phases into three separate compartments, reducing some of the inaccuracy associated with standard flow cytometric phase analysis[44]. In 1985 Begg *et al.*[179] made use of this technique and developed an algorithm to calculate cell kinetic data from a single biopsy following a pulse label of BrdU. A cohort of cells are labelled *in vivo* or *in vitro* and several hours later a single sample or biopsy is taken and fixed. Following disaggregation, denaturation, exposure to the anti-BrdU monoclonal antibody and PI staining, dual measurement flow cytometric analysis can detect the labelled cohort of cells, determine their mean DNA content and thereby calculate Ts.

The problem of heterogeneity of colorectal tissue with regard to kinetic measurements, specifically Tpot, has been addressed recently by Wilson *et al.*[180]. There is also evidence that the denaturation step, a prerequisite for BrdU detection, may cause alteration in the proportion of cells in different phases of the cell cycle[181] and that these changes may be maximal at a denaturation intensity which is tumour specific[122]. The denaturation step may, therefore, need to be optimized for each tumour, a process which is both time consuming and wasteful of tumour tissue; it will further detract from the attractiveness of the technique.

Conclusions

The role played by cell proliferation in the malignant transformation and subsequent growth of colorectal tumours is obviously complex. Most studies of colorectal tumours have examined clinically detectable lesions that have already advanced considerably along their growth curve. There is little information available on the cell kinetic changes that occur in the early stages of tumour development or on why abnormal cells are allowed to proliferate and to escape the body's defence mechanisms. There is considerable evidence that malignant colorectal cells may not cycle any faster than their normal counterparts. Thus, it seems certain that a reduction in the rate of cell loss may play a significant part in the growth of colorectal tumours, a phenomenon which is difficult to quantify. Continuing studies on the role of apoptosis in the development of adenomas and carcinomas may improve our understanding of the kinetic changes that occur in colorectal carcinogenesis.

Acknowledgements

This work was supported by the Cancer Research Campaign and Medical Research Council. R.G., R.W. and N.A. were supported by Royal Victoria Hospital Clinical Research Fellowships and K.W. by DHSS grants.

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British Journal of Surgery 1996, 83, 750–754

Routine preoperative infusion cholangiography at elective cholecystectomy: a prospective study in 694 patients

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The role of preoperative infusion cholangiography (PIC) before elective cholecystectomy has yet to be defined. Between 1985 and 1991 PIC was performed routinely in 694 patients with median (range) age of 52 (17–85) years with biliary calculus disease 1 or 4 days before elective cholecystectomy. Satisfactory opacification of the biliary system was achieved in 90·1 per cent and mild to moderate adverse reactions to the infusion of contrast medium occurred in 0·9 per cent of patients. Peroperative cholangiography (POC) in 43 of 499 patients with a normal PIC was normal. The presence of common bile duct stones was confirmed in 34 of 36 patients with prominent stones at bile duct exploration and in 8 of 26 with suspected stones at PIC. Bile duct dilatation (median diameter 10 mm) without concomitant stones was seen at PIC and confirmed at POC in 20 patients. Bile duct anomalies were found or suspected in 35 patients at PIC and were confirmed in six by POC ($n = 5$), or during the cholecystectomy making the anomaly incidence 0·9 per cent. Information provided by the PIC was not of crucial importance for safe execution of cholecystectomy in any patient, while a single (minor) bile duct lesion (1 of 694; 0·1 per cent) could be ascribed to severe pericholecystitis. The results of this study suggest that routine PIC is not warranted. However, PIC is an alternative to selective preoperative endoscopic retrograde cholangiography or selective POC. PIC needs to be supported by POC in approximately 20 per cent of patients (in case of absent or poor opacification of the bile ducts or suspicion of stones or anomalies at PIC).

Peroperative cholangiography (POC) has been an essential adjunct to open cholecystectomy. It has been advocated to be performed either routinely[1–4] or selectively[5–13] in order to detect bile duct calculi or anomalies, to avoid unnecessary bile duct explorations (BDEs) and retained stones as well as peroperative duct lesions. Preoperative intravenous cholangiography (PIC) has been applied less frequently in conjunction with elective cholecystectomy. Patients with bile duct stones can be identified by clinical features[10,13–18], liver function tests[10,12,15–20] or peroperative findings[10,13,14,16,18,19]. In recent years preoperative[21–24] or postoperative[23,25] endoscopic retrograde cholangiography (ERC) has also been advocated in connection with laparoscopic cholecystectomy in order to identify and treat patients with bile duct calculi. However, although there has been a resurgence of interest in PIC, it has not gained proper recognition in the authors' opinion and deserves further study. In addition to a prospective randomized study of PIC *versus* POC performed in this department[26], five other studies of PIC have been reported in recent years[27–31]. Only two studies comprise more than 100 patients[28,30]; further studies of PIC have been sought[32,33] and it has been suggested that its role should be reconsidered[34]. Based on early experience from this department[26] routine PIC was prospectively performed to further evaluate this diagnostic strategy in conjunction with elective cholecystectomy.

Patients and methods

Between 1985 and 1991 cholecystectomy was performed in this department in 1576 consecutive patients with biliary calculus disease (*Fig. 1*). In the patients entered into the study PIC was performed on the day before operation (or 4 days before surgery in patients undergoing operation on a Monday). Median (range) age was 52 (17–85) years and the female:male ratio was 2·8:1. The indications for surgery were biliary colic alone ($n = 545$) or associated with a history of cholecystitis ($n = 42$), jaundice ($n = 29$), biliary pancreatitis ($n = 33$), abnormal liver function tests (LFTs) ($n = 42$) or cholangitis ($n = 3$). Some 230 of 694 patients had two or more raised LFTs at the time of surgery.

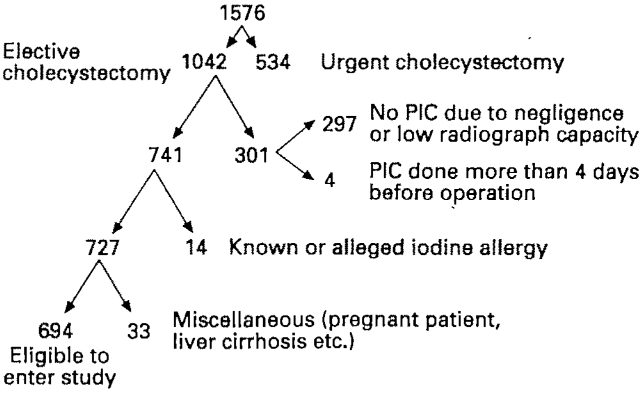
1576
Elective cholecystectomy
1042
534
Urgent cholecystectomy
297
No PIC due to negligence or low radiograph capacity
741
301
4
PIC done more than 4 days before operation
727
14
Known or alleged iodine allergy
694
Eligible to enter study
33
Miscellaneous (pregnant patient, liver cirrhosis etc.)

Fig. 1 Criteria for exclusion of patients from study. PIC, preoperative infusion cholangiography

Preoperative infusion cholangiography. The examination was performed, as previously described[26], with the patient in a 20° right posterior prone position; contrast medium 100 ml (Biliscopin 50 mg I/ml, meglumine iotroxinate; Schering AG, Berlin, Germany) was administered intravenously over 30 min, followed by tomograms of the bile ducts at 5–10 mm intervals using conventional radiographic technique.

Peroperative cholangiography. The bile ducts were opacified following cannulation of the cystic duct by a plastic catheter (Broomé cholangiography catheter; Surgimed A/S, Stenløse, Denmark) and subsequent injection of contrast medium (Omnipaque 200 mg I/ml, iohexol; Nycomed, Oslo, Norway). The examination was performed using a portable radiographic unit

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Paper accepted 3 September 1995

and transmitted to the radiography department as video signals for evaluation of real-time images and to be stored on videotapes.

Bile duct exploration. Supraduodenal approach through a choledochotomy incision was used in all but one of the patients subjected to bile duct exploration. In one patient a stone was removed via the cystic duct. Choledochoscopy was performed in 28 patients (56 per cent) before ($n=4$) or after ($n=21$) exploration or both ($n=3$).

Outcome was assessed in terms of diagnostic yield of the PIC and subsequent need for supportive POC, identification of bile duct anomalies and its impact on the safe execution of cholecystectomy and the incidence of adverse reactions to the infusion of contrast medium.

Statistical analysis Discrete variables were analysed by the χ^2 test and Fisher's exact test for expected small numbers (Winstat computer package; Kalmia, Cambridge, UK). *P* values are given only where differences were significant, taken as $P<0{\cdot}05$.

Results

In 625 patients (90·1 per cent) adequate opacification of the bile ducts was obtained by PIC. In 499 patients the cholangiogram was normal. In 44 of 499 patients POC was performed, without stated indication ($n=29$), because of unclear anatomy during surgery ($n=12$), elevated serum bilirubin ($n=1$), peroperative bile duct injury ($n=1$) or because of peroperative dislodgement of a cystic duct stone into the common bile duct (CBD) ($n=1$). In the patient with a dislodged stone, POC showed a CBD stone; it was normal in the remaining 43. In 128 patients PIC showed abnormal findings as described below.

Bile duct calculus, suspicion of calculus or dilatation of bile duct (Fig. 2)

POC failed to confirm calculi in two patients, one of whom had signs of stone passage the night before surgery. The other patient had BDE despite a normal POC because a stone was seen through a translucent bile duct wall. In one patient, by mistake, neither POC nor BDE was performed.

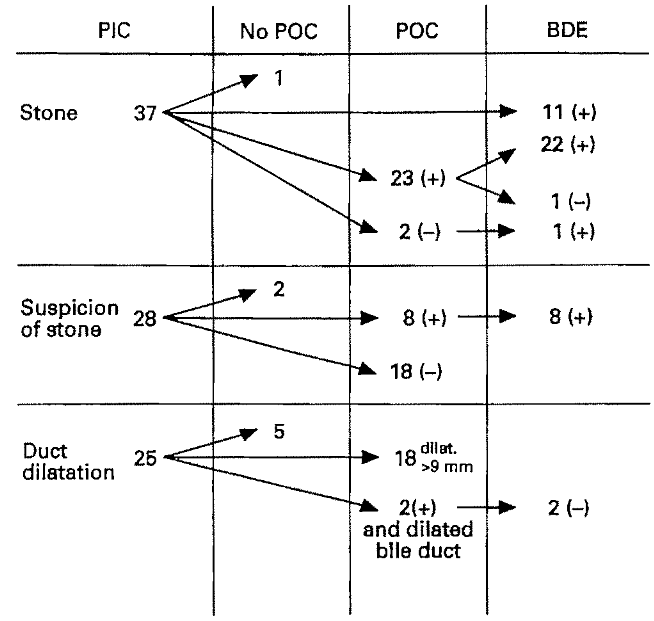

Fig. 2 Findings in patients with stones, suspicion of stones or dilated bile ducts at preoperative infusion cholangiography (PIC). +, stone; −, no stone. POC, peroperative cholangiography; BDE, bile duct exploration

Two patients with suspected stone had neither POC nor BDE. One had a stone impacted in the gallbladder neck and the other had a small fibrotic gallbladder with an accidental peroperative minor lesion of the first part of the duodenum. Median (range) diameter of the CBD in patients with dilated (greater than 5 mm) ducts was 10 (6–20) mm.

Bile duct stricture

In three patients PIC showed a narrow termination of the CBD. POC was, however, normal.

Bile duct anomaly

Anomalies of the biliary tract were found or suspected in 35 patients with ($n=2$) or without ($n=33$) concomitant bile duct stones. In 14 patients a low fusion of the dorsocaudal branch to the common hepatic duct (CHD) was suspected. Six patients underwent POC which confirmed the anomaly in four. The remaining eight patients did not undergo POC because no anomalies were encountered ($n=7$) or the anomaly was confirmed ($n=1$) when cholecystectomy was carried out. In 13 patients a distal ($n=8$) or proximal ($n=5$) branching of the cystic duct from the CHD was suspected at PIC. A distal junction of the ducts was confirmed in one of four patients subjected to POC while nine had operation which did not reveal any abnormal anatomy. In three patients without and two with CBD stones a distal junction of the right and left hepatic ducts was suspected but could not be verified at POC. In two patients an aberrant bile duct and an indentation in the right hepatic duct respectively, were suspected on PIC. In the former patient no abnormal duct was detected at cholecystectomy and in the latter POC was normal. One patient with unclear bile duct anatomy on PIC had a normal POC.

Failure to obtain satisfactory opacification of the biliary system at PIC (Fig. 3)

In two patients without delineation of the termination of the CBD, POC was not performed because of a solitary gallbladder calculus and narrow cystic duct. Six patients with non-opacified bile ducts had no POC because of adverse reactions to the contrast medium at PIC ($n=2$), impacted stone in the gallbladder neck ($n=2$), gross inflammation in the hepatoduodenal ligament (subacute cholecystitis) ($n=1$), or normal LFTs ($n=1$).

Adverse reactions to infusion of contrast medium

Six patients (0·9 per cent) experienced adverse reactions to PIC, including hypotension ($n=2$), dyspnoea ($n=1$), rash ($n=2$) and vomiting ($n=1$). Four patients required treatment by antihistamine and/or steroid injections and responded promptly to treatment. According to Ansell *et al.*[34] the allergic reactions were classified as minor or moderate.

Bile duct exploration

Postoperative T-tube cholangiography was performed a median (range) of 4(1–9) days after surgery in 35 of 46

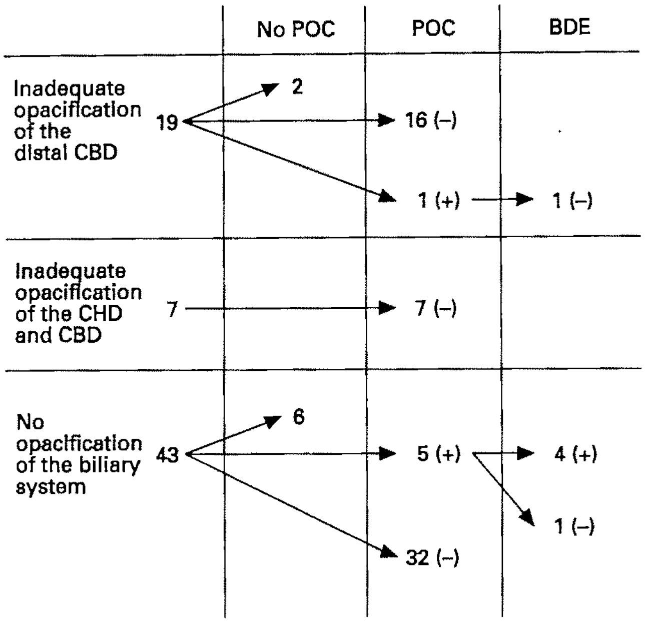
No POC
POC
BDE
Inadequate opacification of the distal CBD
19
2
16 (–)
1 (+)
1 (–)
Inadequate opacification of the CHD and CBD
7
7 (–)
No opacification of the biliary system
43
6
5 (+)
4 (+)
1 (–)
32 (–)

Fig. 3 Findings in patients with no or inadequate opacification of the biliary system at preoperative infusion cholangiography. +, stone; –, no stone. CBD, common bile duct; CHD, common hepatic duct; POC, peroperative cholangiography; BDE, bile duct exploration

Table 1 Findings in patients who underwent additional peroperative cholangiography and/or bile duct exploration ($n = 144$)

Finding at PIC (n)		POC ± BDE (n)	Finding confirmed by POC ± BDE (n)		Predictive value of PIC (%)
Normal	43	43	Normal	43	100
Abnormal	128	101	Abnormal	68	67
Stone	37	36	Stone	34	94
Suspicion of stone	28	26	Stone	8	31
Dilatation of duct	25	20	Dilatation	20	100
Stricture	3	3	Stricture	0	0
Anomaly	35	16	Anomaly	6	38

PIC, preoperative intravenous cholangiography; POC, peroperative cholangiography; BDE, bile duct exploration

patients in whom stones were retrieved from the bile ducts at exploration. Retained calculi were revealed in two patients (6 per cent). In the remainder no postoperative cholangiography was performed because of primary suture of the choledochotomy ($n = 8$), dislodgement of T drain ($n = 2$) or transcystic exploration ($n = 1$). Both patients with retained stones had undergone choledochoscopy.

Discussion

Along with the introduction of laparoscopic cholecystectomy there is renewed interest in the preoperative identification of patients harbouring bile duct calculi[27,35–38] and whether peroperative cholangiography should be performed routinely[39,40] or selectively[30,34,35,38,41,42]. ERC has been included in the diagnostic armamentarium and suggested to be applied before[21–24,35] or after[23,25] surgery. Except for two studies[27,30] there has been little interest in the value of PIC in conjunction with laparoscopic cholecystectomy.

Yield and accuracy of PIC

Infusion yields high density of the contrast medium and satisfactory bile duct opacification in 92·2–94·7 per cent of patients[26,28–30], figures comparable to the 90·1 per cent in this study. PIC has been shown to be disappointing in accurately outlining bile duct pathology with high rates of false-positive (low positive predictive value of 26 per cent[16]) and false-negative (low negative predictive value of 22[31], and 50 per cent[30]) cholangiograms. These series were, however, small and the technique of PIC was either not stated or the contrast medium was administered over 20 min only. No false-negative cholangiograms were found in this study (*Table 1*). Despite the small number of patients (43 of 499; 8·6 per cent) with a normal PIC who had a complementary POC a normal PIC can be regarded as evidence for a normal bile duct, as all these POCs were normal. However, the positive predictive value of PIC was found to be 31 per cent (14 of 45) in 45 patients with suspicion of bile duct calculus, stricture or anomaly subjected to additional POC and/or BDE. These findings emphasize previous experience that PIC provides less detailed information about abnormal biliary systems than does POC.

Bile duct calculi and bile duct dilatation

The higher incidence of CBD calculi in all but one similar study[26–31] (2·5–14 *versus* 7 per cent in this study) might be explained if stones were overlooked on the normal PICs in this study. Another explanation, which is believed to be correct, is the greater rate of factors associated with increased risk of CBD calculi in these studies compared with this study (history of jaundice, cholecystitis and pancreatitis in 35 *versus* 15 per cent, cholecystitis and pancreatitis recently before surgery in 19 *versus* 0 per cent and a mean time of 91 *versus* 1·8 days between PIC and surgery). The negative predictive value of PIC and the positive predictive value of PIC for prominently appearing CBD calculi was 22–91 and 90 per cent[28] respectively, in these studies as compared with 100 and 94 per cent in this series.

Twenty patients in this study (3 per cent) had dilated bile ducts without concomitant stones confirmed by POC. A similar figure (2·1 per cent) has been registered by others[16]. In the case of significant biliary obstruction (impacted calculi) as cause of the dilatation marked elevation of the LFTs in these patients might be anticipated as compared with patients with floating calculi or normal bile ducts. However, the number of patients with normal or a single raised LFT at surgery was 334 of 499, 14 of 23 or 25 of 46 in patients with normal PIC, dilated bile ducts or CBD stones, respectively (P not significant).

Bile duct anomalies and accidental duct lesions

The lack of[27–30] or low incidence of (0·8 per cent)[26] bile duct anomalies in previous studies of PIC has raised doubts regarding the ability of PIC to reveal surgically important anomalies which have been estimated to occur in as many as 4 per cent[5] to 10 per cent[43] of patients subjected to cholecystectomy. The rationale for performing PIC routinely in order to avoid the bile duct injury would be outlining of the biliary tree and detection of bile duct anomalies before dissection of the hepatoduodenal ligament to obtain a transcystic cholangiogram, a potentially hazardous procedure[44]. The cause of accidental peroperative bile duct lesions in the presence of a bile duct anomaly has been reported to be the cystic duct crossing the CBD ($n = 11$) or branching from the left hepatic duct ($n = 1$)[44]. These anomalies might very well have been detected by PIC considering the experience from this study. Undiscriminating reliance on PIC is unwise[28,32] and is no substitute for careful surgical dissection, especially when 39 of 55 bile duct injuries have been reported to occur in patients with normal bile duct anatomy[44].

The only (minor) accidental bile duct lesion in this study (1 of 694; 0·1 per cent) healed uneventfully and was associated with severe pericholecystitis, quite contrary to the experience of others[44]. Bile duct anomalies were suspected in 35 but could be confirmed in only six patients (0·9 per cent), a figure comparable to the registered incidence of 0·8 per cent anomalies in the previous study from this department[26].

The knowledge gained from PIC of a possible anomaly might have made the surgeon excessively careful when dissecting the triangle of Calot and may thus have prevented a bile duct injury. However, in only one patient was an anomaly encountered which was easily identified at cholecystectomy. Hence, it is likely that the information provided by PIC did not enhance the safety of the operations. In consequence, the concern about PIC being unable to reveal surgically important anomalies is not supported by the results of this study and seems to be unjustified.

These results suggest that PIC performed routinely has to be supported by POC in approximately 19·5 per cent (135 of 694) of patients when there is suspicion of stones, anomalies or strictures ($n = 66$) or when opacification of the biliary system is poor or absent on PIC ($n = 69$).

Adverse reactions to the contrast medium

In this study the incidence of adverse reactions to PIC was low (0·9 per cent) and comparable to the experience from previous studies of PIC in this department[26,45]. Furthermore, they were classified as mild to moderate. Similar favourably low complication rates of 0 per cent[29,46] or 1·3 per cent[28,30] of infusion cholangiography have been reported by others but a higher rate of 2·0 per cent has also been recorded[27].

Conclusions

The 9·9 per cent opacification failure rate or 0·9 per cent rate of side-effects, which were mild to moderate, should not be issues *per se* when considering PIC. These results indicate that PIC should be an alternative to selective preoperative ERC or selective POC in patients with increased risk of harbouring CBD calculi.

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British Journal of Surgery 1996, **83**, 755–757

Intravenous infusion cholangiography for investigation of the bile duct: a direct comparison with endoscopic retrograde cholangiopancreatography

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Laparoscopic cholecystectomy has led to an increase in preoperative endoscopic retrograde cholangiopancreatography (ERCP) for the investigation of bile duct stones. ERCP and intravenous infusion cholangiography (IIC) were compared in 111 consecutive patients without jaundice considered to be at high risk for bile duct stones. Both investigations were successfully completed in 100 patients. IIC and ERCP demonstrated a normal bile duct in 81 patients and bile duct stones in 16 patients. IIC failed to identify bile duct stones in two patients (1·8 per cent). IIC was 89 per cent sensitive and 99 per cent specific for detecting bile duct stones in patients without jaundice. It is suggested that IIC is a cost-effective preoperative investigation for bile duct calculi.

The identification of bile duct stones has always been controversial and laparoscopic cholecystectomy has resulted in an increase in the number of preoperative endoscopic retrograde cholangiopancreatography (ERCP) examinations. Many surgical units perform operative cholangiography on all patients undergoing elective open cholecystectomy[1]. Operative cholangiography during laparoscopic surgery can be difficult despite improvements in technique and may add to the length of the procedure[2]. Selective preoperative ERCP in patients at high risk of bile duct stones has become the investigation of choice in some units[3,4], but is invasive and expensive with significant morbidity and mortality rates[5,6]. Intravenous cholangiography has been considered hazardous because of reactions to contrast media[7,8]. The newer technique of slow intravenous infusion cholangiography (IIC) using meglumine iotroxate is reported to be safe, simple to perform and inexpensive[9–12]. The aim of this study was to assess constant IIC for the investigation of the bile duct in selected patients, using ERCP as a 'gold standard'.

Patients and methods

A total of 111 consecutive patients with cholelithiasis but no jaundice considered to be at high risk of bile duct calculi were included in the study. There were 69 women and 42 men with a median age of 54 (range 22–90) years. Selection of high-risk patients included one or more of the following criteria (*Fig. 1*)[3]:

1. A history of obstructive jaundice but no jaundice when entered into the study. Patients with obstructive jaundice at presentation underwent ERCP without IIC and were not included.
2. Acute pancreatitis.
3. A dilated bile duct (greater than 6 mm) or bile duct stones on ultrasonography.
4. Abnormal liver function tests at presentation (serum bilirubin more than 30 umol/l or serum alkaline phosphatase greater than 250 units per litre).

A signed consent was obtained from all patients.

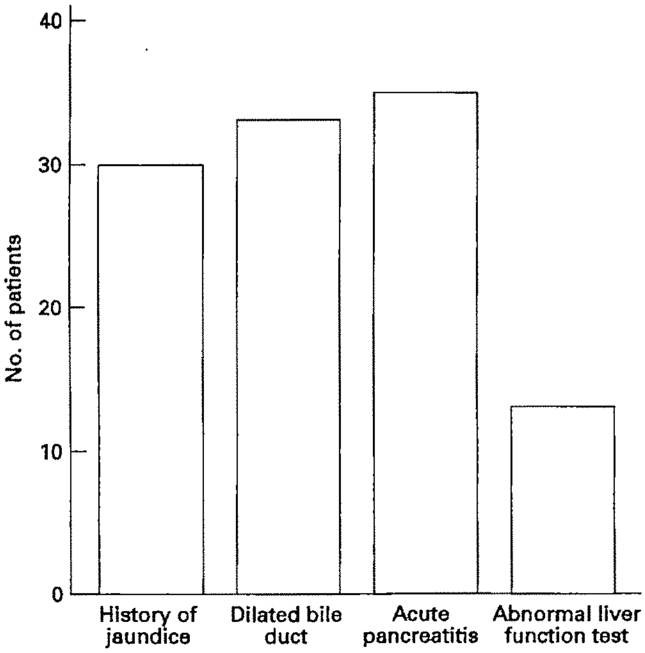

Fig. 1 Indications for intravenous infusion cholangiography and endoscopic retrograde cholangiopancreatography

IIC was performed in all patients using a 2-h infusion of meglumine iotroxate (Biliscopin; Schering, Healthcare, Burgess Hill, UK) 5 g in 500 ml 5 per cent dextrose followed by a plain abdominal radiograph and two tomograms. ERCP was performed within 24 h of IIC using intravenous sedation, a side-viewing duodenoscope and radiography facilities so that each patient acted as his or her own control. These procedures were performed by two clinicians with an interest in ERCP. The IIC and ERCP films were analysed by a consultant radiologist without knowledge of the patient's name or final duct status.

Results

Some 111 consecutive patients were entered into the study. Thirty patients had a past history of jaundice but 21 of these had a normal diameter bile duct on ultrasonography. In three patients (2·7 per cent), IIC failed to demonstrate the biliary tree in sufficient detail and in eight (7·2 per cent), ERCP was unsuccessful because of failure to cannulate the common bile duct. Both

Paper accepted 27 October 1995

Table 1 Intravenous infusion cholangiography compared with endoscopic retrograde cholangiography in the detection of common bile duct stones

	IIC	
	Positive	Negative
ERCP		
Positive	16	2
Negative	1	81

ERCP, endoscopic retrograde cholangiopancreatography; IIC, intravenous infusion cholangiography. Sensitivity of IIC = 89 per cent; specificity = 99 per cent, positive predictive value = 94 per cent; negative predictive value = 98 per cent

investigations were therefore successfully performed in 100 patients. There were no adverse reactions to the intravenous contrast medium; three patients developed mild acute pancreatitis following ERCP which settled but prolonged hospital stay by 3–5 days.

IIC and ERCP were both reported as normal in 81 patients, and no ductal anomalies were detected by either investigation. In 16 patients both procedures detected dilated extrahepatic bile ducts containing stones (*Table 1*). In four patients, IIC was reported as normal but ERCP indicated a dilated bile duct. Stones were present in only two of these four patients (false negatives). IIC indicated bile duct stones in one patient but ERCP showed a dilated duct only (false positive). IIC therefore had a sensitivity of 89 per cent and a specificity of 99 per cent compared with ERCP.

Of the 18 patients identified as having bile duct calculi, ultrasonography demonstrated stones in ten patients, a dilated bile duct but not stones in three and no abnormality in five. In addition, a dilated bile duct was identified on ultrasonography in 24 patients in whom no duct stone was ultimately found.

Discussion

Laparoscopic cholecystectomy has become the procedure of choice for symptomatic gallbladder disease but the method of identification of bile duct calculi has altered. It was common practice to perform operative cholangiography on all patients undergoing open cholecystectomy[1]. Laparoscopic cholangiography, although a well established technique[13], may be technically difficult and has led many surgeons to adopt a selective policy to identify bile duct stones. This policy may reduce operating time and allow planning of theatre lists. However, bile duct stones found by laparoscopic cholangiography may result in conversion to an open procedure, laparoscopic exploration of the bile duct or postoperative endoscopic management[3]. In many units patients at risk of bile duct calculi are selected according to established criteria and undergo preoperative ERCP[3,4]. Low-risk patients are not investigated before operation and probably have less than a 5 per cent chance of presenting with a bile duct stone after cholecystectomy[14].

Diagnostic ERCP is an invasive procedure associated with a 5 per cent incidence of pancreatitis and a global mortality rate of 0·08 per cent[15]. This study directly compared ERCP with infusion cholangiography in 100 patients at risk for bile duct stones in the same 24-h period. Thus all patients acted as their own control. IIC correctly identified bile duct stones in 16 of 18 patients, leaving two patients with false-negative results. Some 81 of the 100 patients had a normal common bile duct demonstrated by both investigations and may suggest that the authors' selection criteria are too wide resulting in overinvestigation of these patients. The selection criteria are being reassessed, and it should be noted that only one patient of the 35 included with a history of acute pancreatitis was ultimately found to have a bile duct stone. There was one false-positive IIC examination which would have resulted in one unnecessary ERCP investigation whereas 81 patients could have avoided preoperative ERCP after normal IIC.

Ultrasonography alone was neither sensitive nor specific enough to detect bile duct stones before operation, as five of the 18 patients with duct stones had a normal appearance on ultrasonography and 24 patients suspected to have dilated ducts on ultrasonography were subsequently shown to be normal. This is in accordance with previous studies[16].

Intravenous cholangiography has been unpopular in the past because of reactions to the contrast media. Most reactions occurred with iodopamide, the older contrast reagent which was usually given by a hand-held injection[8]. The incidence of reactions to the more recently developed meglumine iotroxate is reported to be minimal[9–12] but no long-term evaluation has been carried out. In this series, there were no adverse reactions nor were there any reported in other series using this reagent[17,18]. A large series reporting nearly 700 examinations showed mild or moderate reactions in less than 1 per cent[19]. These studies confirm our belief that the morbidity and mortality rates for IIC are less than those reported for ERCP.

The cost of IIC is approximately £50 requiring an outpatient visit to the radiography department for three plain radiographs. This contrasts with ERCP which requires an overnight stay, medical expertise and costs at least UK £500.

It is suggested that IIC is a sensitive and specific investigation for bile duct stones in patients without jaundice. Patients at low risk for bile duct stones should have no preoperative investigation, whereas high-risk patients should have infusion cholangiography. When IIC shows calculi or an equivocal result, patients should proceed to preoperative ERCP and sphincterotomy if required. This policy may allow an 80 per cent reduction in the number of ERCP examinations along with reduced morbidity and mortality rates. In addition, there would be a significant cost benefit by increasing the ratio of therapeutic to diagnostic ERCP investigations.

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British Journal of Surgery 1996, 83, 758–761

Resection of hepatocellular carcinoma in patients with cirrhosis

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Between 1987 and 1993, 53 hepatic resections for hepatocellular carcinoma (HCC) were performed in 51 patients with cirrhosis. Limited hepatic resection was performed in 66 per cent of patients. The postoperative mortality rate was 13 per cent. The tumours recurred in 27 patients (53 per cent), and the cumulative recurrence rate at 1 and 4 years was 41 and 89 per cent, respectively. Mean time to recurrence was 11·7 months and the most frequent site was the liver (21 patients). The only significant risk factor for recurrence was symptomatic tumours. The recurrence rate of HCC in patients with cirrhosis with surgical resection alone is high and actuarial survival at 4 years is very low. Other approaches to the treatment of HCC in patients with cirrhosis require consideration.

Hepatocellular carcinoma (HCC) is a common complication of hepatic cirrhosis[1]. Frequent monitoring with ultrasonography and of α-fetoprotein (AFP) levels have made it possible to discover small tumours, particularly in patients with cirrhosis or chronic viral hepatitis[2]. Surgical resection by partial hepatectomy or liver transplantation are the only potentially curative treatments[3–6]. However, partial hepatectomy can only be offered to patients with good liver function and well defined, solitary, peripherally-located tumours approachable by limited hepatic resection. Liver transplantation is the only option in patients with poor liver function or in non-resectable tumours, provided extrahepatic malignancy has been ruled out.

The present study details experience gained in surgical resection of HCC in patients with cirrhosis.

Patients and methods

Patients

Between July 1987 and December 1993, 51 patients with cirrhosis underwent 53 hepatic resections for HCC. Their clinical features and demographic characteristics are summarized in *Table 1*.

Thirty-five (66 per cent) patients were asymptomatic, with HCC being discovered by ultrasonography during routine follow-up for cirrhosis. The remaining 18 (34 per cent) were symptomatic. Abdominal pain, toxic syndrome and upper gastrointestinal haemorrhage were the most frequently presenting symptoms.

Ultrasonography before operation detected a single nodule in 49 patients, with a mean(s.d.) size of 3·8(2·2) cm, and detected two nodules in four patients with a mean(s.d.) size of 5·2(1·6) cm. Abdominal computed tomography (CT) with intravenous contrast performed in 34 patients showed: no HCC in four patients, a single nodule with satellites in one, two nodules in two, three nodules in two and a single nodule in all remaining patients. Selective hepatic angiography was performed in eight patients and nuclear magnetic resonance was used in five. Fine-needle aspiration cytology (FNAC) to confirm HCC was performed in 44 patients and was positive in 39.

All patients fulfilled the criteria for a well defined tumour suitable for hepatic resection and good liver function by the Child–Pugh classification (grades A or B).

Paper accepted 4 September 1995

Table 1 Clinical and surgical features

Mean(s.d.) age (years)	63(7) (range 41–76)
Sex (m:f)	44:9 (4·8:1)
Aetiology	
Alcoholic	11 (21)
Postnecrotic HBV	4 (7)
Postnecrotic HCV	29 (55)
Postnecrotic HBV and HCV	1 (2)
Other	8 (15)
Child–Pugh classification	
A	49 (92)
B	4 (8)
Symptoms	
Yes	18 (34)
No	35 (66)
Mean(s.d.) AFP (ng/ml)	333(1172) AFP (ng/ml)
Less than 10 ng/ml (%)	35
10–200 ng/ml (%)	38
More than 200 ng/ml (%)	27
Types of hepatic resection	
Tumorectomy-segmentectomy	35 (66)
Bisegmentectomy	10 (19)
Partial hepatectomy	8 (15)
Additional surgical techniques	22 (42)
Cholecystectomy	17
Portocaval shunt	2
Other	5

Values in parentheses are percentages unless otherwise stated. HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein

Surgical technique

A right subcostal incision extended to the left was performed in 92 per cent of patients and only three had a midline laparotomy (one combined with a subcostal incision). Right thoracotomy with diaphragmatic incision was performed to avoid abdominal adhesions in another patient with several previous laparotomies and a tumour located at the hepatic dome.

Intraoperative ultrasonography was performed in 49 patients. At operation the tumour could not be located by inspection or palpation in 13 (25 per cent) patients but was found by intraoperative ultrasonography. This examination detected additional nodules in six patients who had been diagnosed as having a solitary tumour before surgery.

Limited hepatic resection such as tumorectomy (resection of tumour with a minimum of 10 mm of tumour-free liver parenchyma around the tumour) or segmentectomy was performed in most patients, with an additional surgical procedure in 42 per cent (*Table 1*).

A Pringle manoeuvre with mean(s.d.) duration of 21(8; range 9–37) min was employed in 35 patients to decrease bleeding. Fibrin and collagen were employed in nearly all patients to achieve complete haemostasis of the hepatic resection edge. Closed aspiration drains were normally placed but gauze tamponade was used in one patient. Intraoperative transfusion of mean(s.d.) 3·6(2·3) units of red cells was required in 44 patients, mean(s.d.) 4·0(2·5) units of plasma in 31 patients and mean(s.d.) 7·7(1·0) units of platelets in six patients.

Table 2 Histological features

Mean(s.d.) tumour size (cm)	4·3(2·8)
Less than 3 cm	44
3–5 cm	28
More than 5 cm	28
Number of tumours	
One tumour	64
More than one tumour	36
Satellite nodules	
No	72
Yes	28
Differentiation	
Good	62
Moderate	21
Poor	17
Capsule	
Present	79
Absent	21
Capsule invasion	
No	58
Yes	42
Vascular invasion	
No	60
Yes	40
Type of tumour	
Expansive	49
Infiltrative	51
Type of cirrhosis	
Micronodular	11
Macronodular	26
Micro-macronodular	49
Septal	6
Chronic hepatitis	8
Liver dysplasia	
No	38
Yes	62

Values are percentages

Table 3 Recurrence of hepatocellular carcinoma

Incidence	27 patients (53%)
Site	
Lung	1
Bone	5
Liver	21
Nodular neighbouring segment	7
Nodular distant segment	7
Multiple or diffuse	7
Mean(s.d.) time of recurrence (months)	11·7(10·4; range 2–48)
Period of recurrence (months)	
0–12	63*
13–24	30*
More than 24	7*

*Values are percentages

Histology

Mean(s.d.) tumour size of asymptomatic and symptomatic patients was 3·6(1·7) and 5·1(3·4) cm respectively; this difference was not statistically significant (*Table 2*).

Patients were staged[7] as: T1 in three patients, T2 in 24, T3 in 21 and T4 in five.

Follow-up

α-Fetoprotein measurements and ultrasonography studies were performed every 3–4 months in all patients to detect possible HCC recurrence.

Risk factors for recurrence

Recurrence of HCC in relation to clinical and pathologic characteristics of tumour and cirrhosis was evaluated. These included sex, age, aetiology, alcoholism, hepatitis C virus, hepatitis B surface antigen, symptoms, AFP, type of resection, tumour size, number of tumours, type of tumour, satellite nodules, tumour differentiation, tumour capsule, capsule invasion, vascular invasion, type of cirrhosis and liver dysplasia.

Statistical analysis

All data are expressed as mean(s.d.) and comparisons between the means were made by Student's *t* test or Mann–Whitney U test for parametric and non-parametric analysis. χ^2 and Fisher's exact probability test, where appropriate, were used to compare the incidence of recurrence among groups. Survival rate and cumulative recurrence rates after resection were estimated for each variable by the Kaplan–Meier method and the log rank test. Values were considered significant at $P < 0{\cdot}05$.

Results

Morbidity and mortality

There were seven (13 per cent) deaths after surgery (less than 30 days). Liver failure was the cause of death in four, bronchoaspiration in one, septicaemia in one and bleeding in one.

Ascites occurred in 51 per cent of patients. Progressive hepatorenal syndrome developed in one patient. Other major complications occurring in 28 per cent of patients included upper gastrointestinal bleeding, subphrenic abscess, abdominal wound dehiscence and hepatic failure.

Mean(s.d.) postoperative stay was 13·1(8·9; range 1–53) days.

Recurrence of HCC

Follow-up ranged from 1 to 63 (mean(s.d.) 17 (14·2)) months. Tumour recurrence was diagnosed in 27 patients (53 per cent), and the most frequent site of recurrence was the liver with three different patterns. These were either a single nodule in a neighbouring segment, a single nodule in a distant segment or multinodular recurrences (*Table 3*). Mean time to recurrence was 11·7 months. Only two patients had tumour recurrence later than 24 months after surgery.

Two patients underwent repeat hepatic resection for a single nodule recurrence, but both died from diffuse recurrence 10 and 3 months later respectively. Liver transplantation was performed in two patients with HCC recurrence; one patient died from infection 8 months later with no evidence of tumour recurrence at necropsy, and lymph node metastasis was found in the other patient after liver transplantation; this patient died from peritoneal carcinomatosis 6 months later. A further five

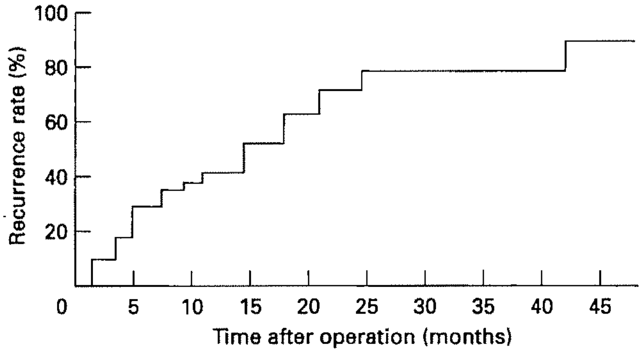

Fig. 1 Cumulative hepatocellular carcinoma recurrence rate

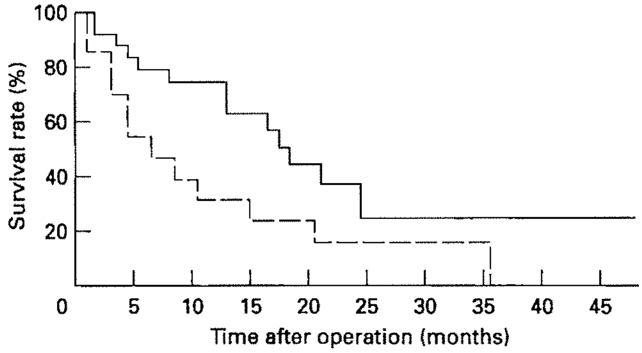

Fig. 2 Disease-free actuarial survival according to symptoms. ———, Asymptomatic; ––––, symptomatic. $P = 0.02$

patients with recurrences were treated with intratumoral instillation of alcohol in one, chemoembolization with lipiodol, adriamycin and Gelfoam (Johnson and Johnson, Ascot, UK) in two, and radiotherapy for palliation of pain from rib and vertebral bone metastases in two.

The cumulative recurrence rates at 1, 2, 3 and 4 years are shown in *Fig. 1*.

Risk factors for recurrence

Recurrence rate of HCC was higher in patients with symptomatic tumours than in those with asymptomatic tumours (86 *versus* 43 per cent, $P = 0.01$), in multiple tumours compared with single nodule tumours (80 *versus* 45 per cent, $P = 0.03$) and in tumours with satellites *versus* those without (90 *versus* 47 per cent, $P = 0.03$).

Disease-free actuarial survival was statistically significantly different between symptomatic and asymptomatic patients ($P = 0.02$) (*Fig. 2*).

Follow-up and survival

Twenty-eight patients died during follow-up. The main cause of death was tumour recurrence and liver failure in 18 patients. No recurrence was observed in the remaining ten patients: five died from liver failure, four from septicaemia and one from upper gastrointestinal bleeding.

During follow-up, two patients without recurrence developed liver failure and received liver grafts 4 months and 3 years later respectively.

Mean(s.d.) overall survival of patients surviving operation was 24(3) months and actuarial survival is shown in *Fig. 3*. Mean survival time of patients with and without recurrence was 24 and 27 months respectively and actuarial survival is also shown in *Fig. 3*.

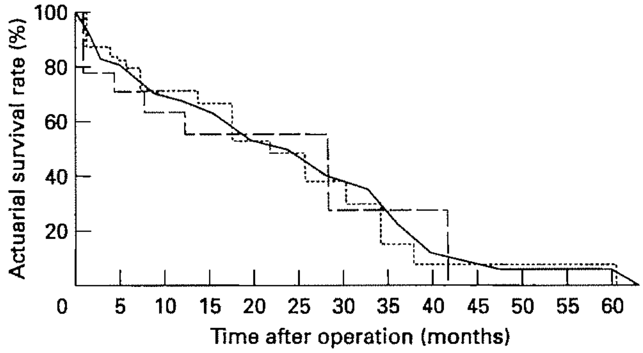

Fig. 3 Actuarial survival rate. ———, General; ––––, no recurrence; ....., recurrence

Mean(s.d.) survival time from diagnosis of tumour recurrence was 8·9(6·7; range 1–25) months. Mean(s.d.) survival was 9·1(5·6) months when the recurrence was treated and 8·8(7·5) months when it was not.

Discussion

Strict follow-up of known patients with cirrhosis, mainly by ultrasonographic examination, has increased the frequency of diagnosis of small resectable HCC in patients with cirrhosis[2,5]. This is reflected in this series by the fact that 66 per cent of patients were asymptomatic, the tumour being detected by ultrasonography.

Intraoperative ultrasonography[8–11] is a valuable tool, not only for detecting the tumour, but also for establishing adequate resection margins sparing as much parenchyma as possible. In this study, 25 per cent of tumours were not found on careful inspection or palpation of the cirrhotic liver but were located with intraoperative ultrasonography examination.

Acceptable morbidity and mortality rates after operation have been obtained with liver resection of HCC in cirrhosis[4–6,8,12–15], although the incidence of tumour recurrence during follow-up is high[16–18]. The recurrence rate in this series was 53 per cent in patients surviving surgery, and was similar to that of others[6,16,19,20]. The cumulative recurrence rate at 3 years was 78 per cent, similar to that found by Belghiti *et al.*[21] who found an intrahepatic tumour recurrence rate of 60 per cent, with a cumulative recurrence rate of 81 per cent at 3 years and 100 per cent at 5 years.

The majority of tumour recurrences were intrahepatic and occurred within the first year after resection, as reported by other authors[19,22]. Most intrahepatic tumour recurrences were single nodules, and only one-third of intrahepatic recurrences were multinodular. It is unknown whether tumour recurrence is a true intrahepatic recurrence of the original tumour or a new tumour that appears in preneoplastic cirrhotic tissue. Several studies suggest that both conditions may exist[23].

The most significant prognostic factors reported for recurrence are: more than one tumour, tumour size more than 2 cm in diameter, and vascular invasion[6,17,19,24,25]. In this series, symptomatic tumours had a statistically higher incidence of recurrence than asymptomatic tumours. Other significant risk factors identified were the presence of more than one nodule or satellite nodules. However, only asymptomatic cases have a significantly lower chance of recurrence. Thus, close follow-up of patients with cirrhosis is important for early detection of asymptomtic HCC.

Tumour recurrence may be treated by different approaches[26] depending on several parameters such as size and location of the tumour, number of nodules and liver function reserve that deteriorates with time. One option to treat recurrence is repeat resection, and survival with a second radical resection may be 75 per cent at 3 years[16]. However, the possibility of performing this second resection is usually low. Furthermore, Ringe *et al.*[27] found a high incidence of HCC recurrence with repeat resection; they proposed liver transplantation in cases of resectable tumour recurrence and achieved better results with this technique. Tumour recurrences may also be treated with chemoembolization[1,6,22,26], with a 2-year survival of 53 per cent. An alternative treatment is intratumoral alcohol instillation[1,26]. When no treatment was possible, the mean survival was 2 months[4].

A different approach to HCC in cirrhosis is to perform liver transplantation[3,6,15,27]. The preneoplastic condition of liver cirrhosis and the appearance of new tumours in the liver may justify resection of the whole liver since, theoretically, the possibility of intrahepatic tumoral recurrence will be reduced.

Patients with cirrhosis with poor liver function (Child grades B and C) with resectable HCC must receive a liver graft as they will fail to tolerate liver resection and will die from liver failure after operation. The prognosis of liver transplantation is directly related to tumour stage, defined by tumour size and lymph node metastasis[6,27]. Survival at 3 years is 50–60 per cent when lymph nodes are negative, and 0 per cent when lymph nodes are positive. These results with liver transplantation are better than those with liver resection in patients with good hepatic function, graded as Child grade A, in whom the incidence of HCC recurrence is very high and the long-term survival low by recurrence and/or liver failure.

The poor results obtained with resection of HCC in patients with cirrhosis in terms of tumour recurrence and patient survival invite reconsideration of the best treatment for patients with HCC and Child grade A cirrhosis.

Acknowledgements

The authors thank Dr Joan Penella for statistical analysis support and Miss Christine O'Hara for valuable revision of the English version of the paper.

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British Journal of Surgery 1996, 83, 762–763

Surgical workshop

Re-reconstruction of a single remnant hepatic vein

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Hepatic vein reconstruction is carried out following hepatectomy for cancer to preserve as much of the remaining liver function as possible[1]. Occasionally, the use of reconstruction allows complete resection of a tumour that involves the confluence of the three major hepatic veins[2]. This report describes repeat hepatectomy[3] combined with two successful reconstructions of a single remnant right hepatic vein at different sites after extended left hepatectomy.

Paper accepted 19 September 1995

Surgical technique

A 36-year-old man who had undergone colectomy with lymph node dissection for sigmoid colonic cancer was referred with a 6-cm liver metastasis involving the confluence of the left and middle hepatic veins. Extended left hepatectomy removing both of the hepatic veins was performed. After 6 months, a 2-cm tumour that invaded a tributary of the right hepatic vein was found deep in segment 5. A second hepatectomy was carried out with reconstruction of the tributary using a 2·5-cm greater saphenous vein graft.

More than 1 year later a 4-cm tumour recurred around the root of the single remaining right hepatic vein. Transhepatic arterial chemotherapy (5-fluorouracil; total dose 20 g) was given but the tumour diameter increased to 8 cm. A third hepatectomy with right hepatic vein re-reconstruction was conducted (*Fig. 1*). Intraoperative ultrasonography confirmed tumour invasion of the hepatic venous trunk and an absence of thick accessory hepatic veins. After mobilizing the liver remnant, the right hepatic venous root and the suprahepatic and infrahepatic vena cava were taped. Using Pringle's occlusion, liver transection was performed with a tumour clearance of over 1 cm. After total parenchymal division of segments 7 and 8, the right hepatic vein was transected, leaving a 2-cm free end at both stumps. A venovenous bypass was then formed between the liver-side stump of the hepatic vein and the infrahepatic vena cava using a 60-cm

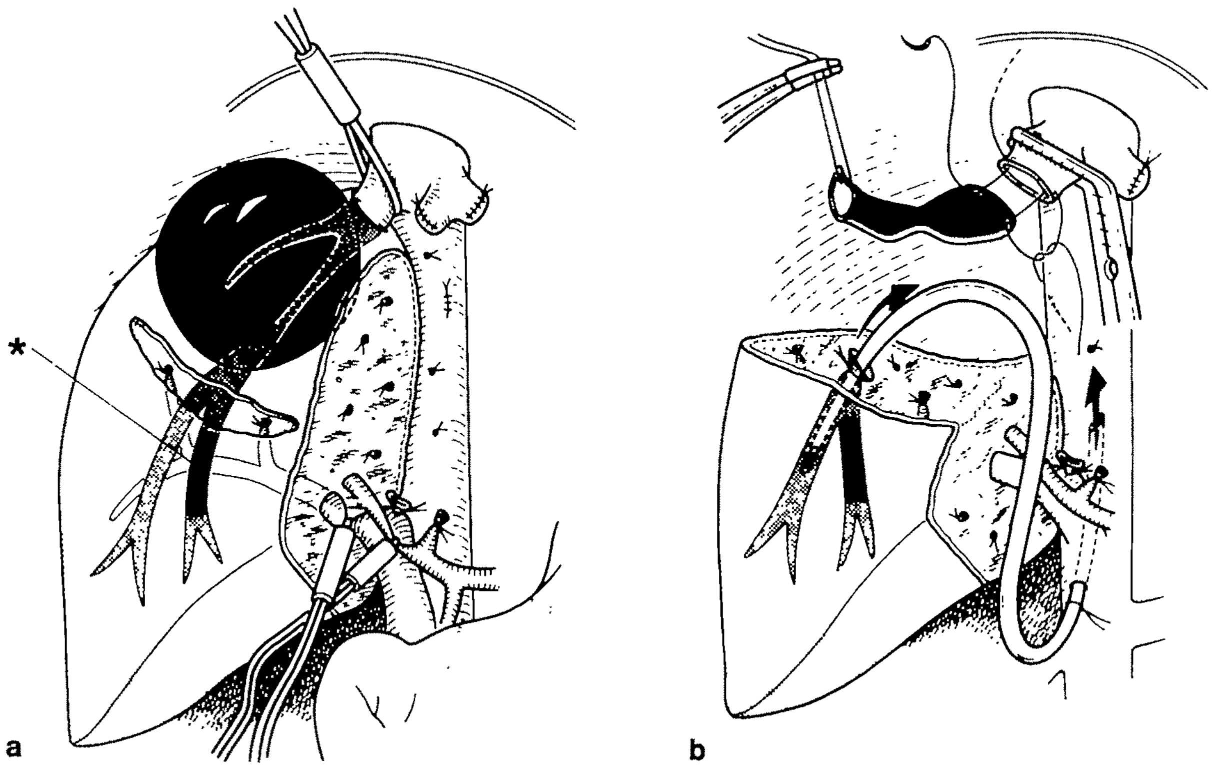

Fig. 1 Right hepatic vein re-reconstruction (asterisk indicates the first reconstruction). **a** Liver transection under inflow and occasional outflow occlusion. **b** Venovenous bypass formation and the second reconstruction using the common iliac vein graft (cava-side anastomosis was established on the bypass without any need for vascular occlusion, while total occlusion was required for liver-side anastomosis)

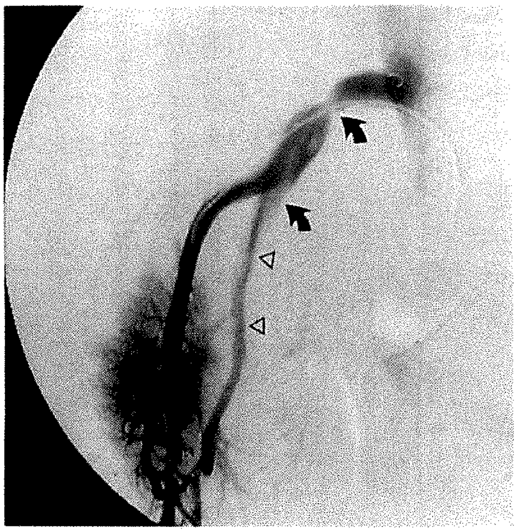

Fig. 2 Postoperative right hepatic venogram (taken 3 months after operation, on right anterior oblique position) showing adequate outflow drainage and the sites of the first (open arrowheads) and second (solid arrows) reconstructions

heparin-coated Anthron Tube (Toray Industries, Tokyo, Japan)[1]. On reperfusion, haemostasis of the raw surface was satisfactory, indicating adequate outflow through the bypass. The right hepatic vein was then reconstructed by anastomosing a 4·5-cm common iliac vein graft (2 cm diameter) with 8/0 polypropylene continuous or interrupted sutures. Both Doppler ultrasonography and venography (*Fig. 2*) confirmed adequate hepatic venous drainage and calibre. The patient made an uneventful recovery with no evidence of liver failure, and remains well after 6 months.

Discussion

This is the first report to document re-reconstruction of a single remnant hepatic vein during repeat hepatectomy for cancer. In this patient the three hepatectomies would have left only segment 6, even with hypertrophy of the remnant. The third hepatectomy required absolutely successful hepatic vein reconstruction to guarantee one remaining outflow tract. The authors know of only one reported case of 'subtotal hepatectomy'[4], where reconstruction was unnecessary owing to the presence of the 'inferior right hepatic vein'[5], which completely drained the residual part of the posterior segment. In the present patient, however, the procedure was the only option because of the lack of such accessory veins. For the second reconstruction the common iliac vein was selected as a graft to match the calibre of the right hepatic venous root, conserving the maximum possible length of the hepatic venous stumps for easy anastomosis, and using a venovenous bypass[1] to minimize congestion of the hepatic parenchyma to be preserved.

This technique has the potential to improve the resectability of liver tumours, although the impact of such procedures on long-term survival needs to be determined.

Acknowledgements

This study was supported in part by a grant-in-aid for cancer research from the Ministry of Health and Welfare of Japan.

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British Journal of Surgery 1996, 83, 764–768

Long-term results of endoscopic stenting and surgical drainage for biliary stricture due to chronic pancreatitis

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A retrospective evaluation was made of the long-term results of endoscopic stenting in 58 patients with benign biliary stricture due to chronic pancreatitis. Immediate relief of jaundice and cholestasis was achieved in all patients after endoscopic stent insertion. Median follow-up was 49 months. Five (9 per cent) of the 58 patients had complications following therapeutic endoscopic retrograde cholangiopancreatography. Late stent-related complications occurred in 37 (64 per cent) of 58 patients. There were no deaths. Sixteen (28 per cent) of the 58 patients had regression of the biliary stricture and permanent removal of the stent. Forty-two patients had persistent biliary stricture: 26 had continued stenting and 16 underwent surgical procedures. Early morbidity after surgery was found in six of 16 patients, with no deaths. Postoperative relief of jaundice was achieved in 15 of the 16 patients. In conclusion, endoscopic stenting and surgery are both effective treatments for biliary stricture in patients with chronic pancreatitis. Endoscopic stenting is associated with fewer early complications. However, late stent-related complications remain a major limitation. Endoscopic stenting offers definitive treatment in more than one-quarter of patients (28 per cent).

Jaundice due to obstruction of the intrapancreatic segment of the common bile duct (CBD) occurs in 3–46 per cent of patients with chronic pancreatitis[1–7]. Persistent cholestasis may lead to recurrent cholangitis in about 9 per cent and to secondary biliary cirrhosis in about 7 per cent of patients. Pyogenic liver abscesses as a result of persistent biliary obstruction have also been described[8]. Therefore, biliary drainage may be indicated[3,5–7,9,10].

Until now, surgical drainage has been the mainstay of treatment in patients with biliary obstruction due to chronic pancreatitis. However, surgical drainage has been associated with considerable morbidity (15–30 per cent; mainly wound infection, biliary leakage, haematoma) and mortality (0–7 per cent[1,9,11–17]) rates.

Endoscopic biliary stenting is an alternative to surgery for the initial treatment of jaundice and cholangitis in these patients. The procedure-related morbidity and mortality rates after biliary stent insertion are low[18–20]. However, stent dysfunction with subsequent recurrent jaundice or cholangitis is a frequent late complication, necessitating regular stent exchanges[18–20]. Whether either endoscopic treatment or surgical drainage should be preferred as a long-term treatment remains a point of discussion.

The long-term results of polyethylene biliary stenting were studied in 58 patients with benign biliary stricture due to chronic pancreatitis. It was decided to perform subsequent surgical bypass procedures in 16 of these 58 patients, who had persistent biliary stricture. The results of surgery in these patients were also evaluated. The aim of the study was to analyse the morbidity and mortality after endoscopic and surgical therapy. A particular interest was to determine how often endoscopic therapy can be definitive treatment, and also in which cases endscopic therapy can be a useful alternative to surgical drainage.

Patients and methods

A retrospective review was made of the records of 58 patients with chronic pancreatitis and biliary stricture, treated by endoscopic stent insertion between 1982 and 1994. There were 46 men and 12 women of median age of 47 (range 19–76) years. The indication for endoscopic stent insertion was persistent jaundice in 46 patients (together with cholangitis in three of 46) and persistent cholestasis in 12. Persistent cholestasis was defined as an increase in the level of alkaline phosphatase to more than three times the normal value for more than 1 month. Chronic pancreatitis was due to alcohol abuse in 43 patients, pancreas divisum in one and was idiopathic in 14. Forty-one (71 per cent) of the 58 patients had chronic calcific pancreatitis. Chronic pancreatitis had been present for a median of 13 (range 1–171) months before biliary stent insertion. Ten patients had had previous pancreatic surgery (pancreaticojejunostomy, three; tail resection, two; drainage of an abscess, one; necrosectomy, one; pseudocyst drainage, three (combined with sphincteroplasty in one patient)). One patient had had a previous laparotomy to perform a biliary bypass, which was not possible for technical reasons.

Diagnostic endoscopic retrograde cholangiopancreatography (ERCP) was performed in all patients. A distal CBD stricture was defined as (1) distal narrowing of the common duct, with (2) proximal dilatation, and (3) delayed runoff of contrast. A polyethylene Amsterdam-type stent (10 Fr) was inserted through the stricture as described previously[21]. A biliary sphincterotomy was performed if necessary to improve access to the CBD before stent insertion. Additional endoscopic therapy was performed at the same session in some patients, including biliary or pancreatic stone removal, pancreatic stenting and pseudocyst drainage.

Patients were re-evaluated 3–9 months after biliary stent insertion. The stent was removed and, if regression of the biliary stricture was found, no new stent was inserted. Regression of the stricture was defined by easy passage of a 6-Fr catheter, followed by good runoff of contrast (drainage within 1–2 min). If significant stricture was still present, a new stent was inserted.

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Stents were exchanged electively every 3–9 months or when patients had recurrent symptoms (jaundice, cholangitis, pain) or cholestasis as a result of stent dysfunction. Patients with cholangitis also had intravenous antibiotic treatment (amoxycillin 4 g/day, gentamicin 4 mg/day). All patients were followed in the outpatient clinic at regular intervals for clinical and laboratory examination.

Surgery was performed if patients had frequent recurrent symptoms as a result of stent occlusion or duodenal stenosis, or if they required pancreatic surgery for persistent chronic pain. If there was a contraindication for surgery (poor general condition, advanced age or portal hypertension), or if the patient refused operation, regular plastic stent exchanges were continued or a self-expanding metal Wallstent (Schneider, Bülach, Switzerland) was inserted.

The prognostic factors for a definitive successful outcome of biliary stenting were evaluated. Successful treatment was defined as (1) clinical improvement, with (2) stricture regression, and (3) permanent removal of the stent. Prognostic factors included alcohol abuse, sex, presentation with jaundice or cholestasis, sphincterotomy, pancreatic duct stenting, age, duration of chronic pancreatitis and duration of biliary stenting.

Statistical analysis was performed with Fisher's exact test and the χ^2 test with Yates' correction for categorical data. Mann–Whitney rank sum tests were used for analysis of continuous data.

Results

The cholangiogram showed a distal biliary stricture with proximal dilatation in 58 patients who had polyethylene stents inserted. Forty-seven patients had biliary sphincterotomy before stent insertion. Concomitant bile duct stones were present in seven patients and were successfully removed endoscopically. The pancreatogram showed pancreatic stones in seven patients and stricture with dilatation of the pancreatic duct in 26. Ten patients had pancreatic pseudocysts (with compression of the CBD in two of these). Endoscopic therapy of a pancreatic lesion was performed in 21 patients including pancreatic stone removal (seven), pancreatic stent insertion (18) and internal pseudocyst drainage (four).

All patients had relief of jaundice and cholestasis within 2 weeks of biliary stent insertion. The serum alkaline phosphatase level decreased from a mean at presentation of 420 (range 50–2570, normal value less than 80) units/l to a mean after endoscopic drainage of 97 (range 48–177) units/l, with complete normalization in 42 per cent. In jaundiced patients, mean serum bilirubin concentration decreased from 163 (range 40–177, normal value less than 17) to 12 (range 5–19) μmol/l.

The overall incidence of complications following therapeutic ERCP was five (9 per cent) of 58. Two patients developed bleeding after extension of a previous sphincterotomy; both received blood transfusions and recovered well. One patient had an exacerbation of pancreatitis and improved with conservative treatment. One patient developed cholecystitis and liver abscesses and underwent cholecystectomy in combination with antibiotic treatment. One patient developed fever of unknown cause and was treated with antibiotics. No patient died from therapy-related causes.

Patients had a median of 3 (range 1–13) stents over a median of 14 months (range 4 days to 99 months). The incidence of polyethylene stent-related complications was 37 (64 per cent) of 58, due to stent clogging in 36 patients, stent migration in four and/or duodenal erosion in one. These patients were successfully treated by stent exchange. Three patients finally had metal Wallstents (one covered, two uncovered) inserted because they had frequent plastic stent dysfunction and surgery was contraindicated. One of the three patients had proximal migration of the covered Wallstent, which was replaced by a polyethylene stent again.

Median follow-up for all patients irrespective of treatment allocation was 4·1 years (range 4 days to 11·2 years) after stent insertion. *Fig. 1* shows the long-term results divided over the various treatment allocations. In 16 (28 per cent) of the 58 patients, regression of the stricture was found at repeat ERCP and stents could be permanently removed after a median of 10 (range 1–31) months (*Fig. 2*). These patients had no recurrent jaundice and cholestasis over a median of 46 (range 3–113) months.

Twenty-six of the 58 patients had persistent stricture and continued biliary stenting over a median of 19 months (range 4 days to 99 months). The reasons for continuing stent treatment were contraindication for surgery in six patients and a preference for non-surgical treatment in 14. A further two patients were lost to follow-up and four died from pulmonary carcinoma (one), myocardial infarction (one), liver failure due to cirrhosis (one) and adult respiratory distress syndrome (one).

Table 1 shows prognostic factors associated with a definitive successful outcome of biliary stenting. No significant difference was found between alcoholics and non-alcoholics, men and women, sphincterotomy and no sphincterotomy, pancreatic stenting and no stenting. The success of biliary stenting was higher in patients with isolated cholestasis when compared with jaundiced patients, although the difference was not statistically significant. The mean age and duration of pancreatitis were lower in patients with successful endoscopic stenting compared with those without success. The mean duration

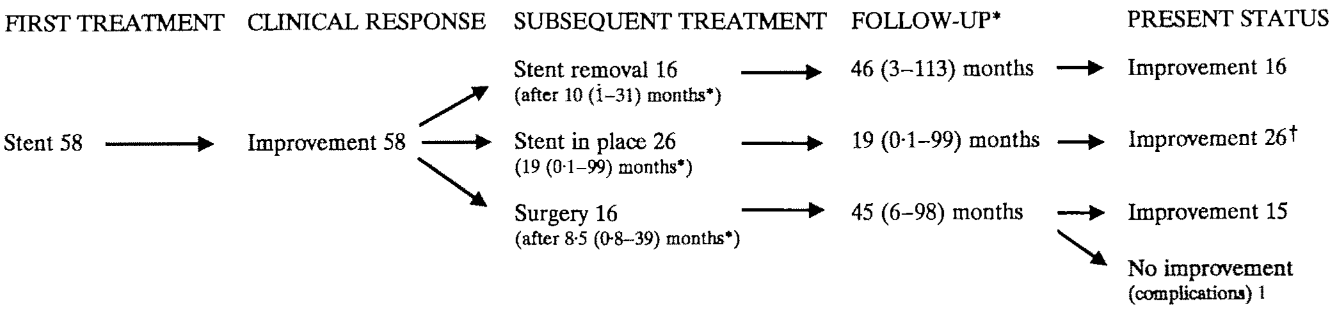

Fig. 1 Long-term results of endoscopic therapy and subsequent surgical drainage. *Values are median (range); †two patients were lost to follow-up and four died

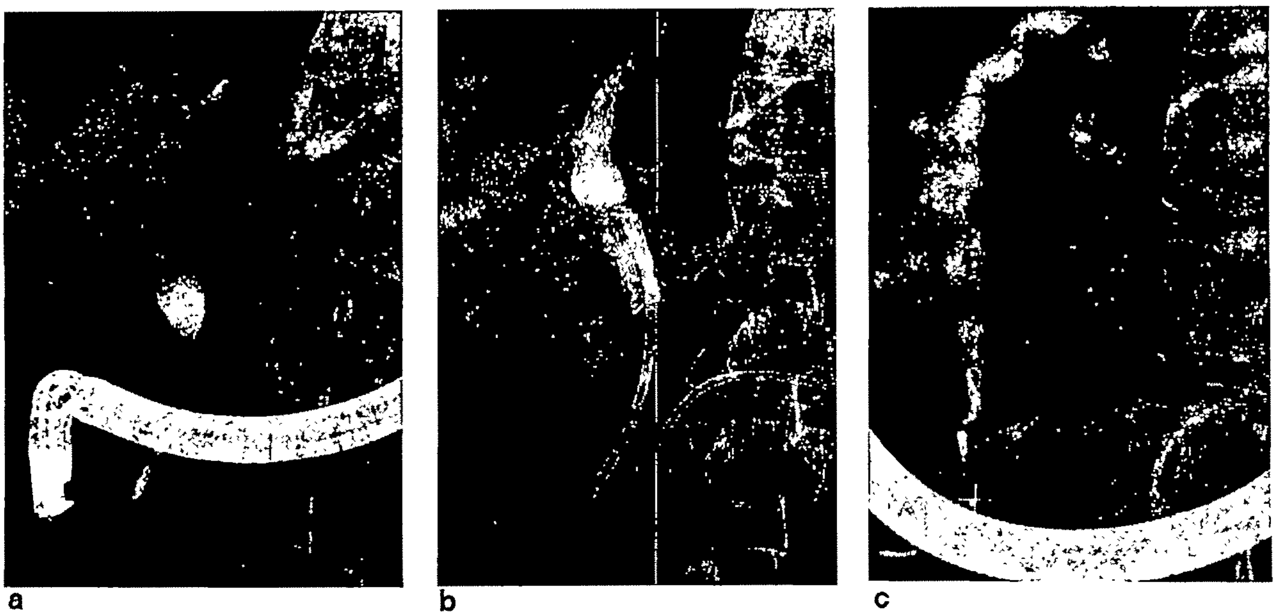

Fig. 2 A 36-year-old man, with known chronic alcoholic pancreatitis, presented with jaundice and recurrent abdominal pain. a Cholangiogram showing a smooth distal stricture in the intrapancreatic portion of the common bile duct with prestenotic dilatation. A pancreatic stent was inserted for a stricture in the pancreatic duct. b Subsequently a biliary stent was inserted. c After 2 months the patient had relief of symptoms, regression of the biliary stricture was found and both stents were removed permanently (follow-up 73 months)

Table 1 Prognostic factors for definitive success of biliary stenting in 58 patients

	Successful treatment ($n = 16$)	No success ($n = 42$)	P*
Alcoholic	10	33	0·31
Not alcoholic	6	9	
Male	13	33	1·0
Female	3	9	
Jaundice	10	36	0·07
Cholestasis	6	6	
Sphincterotomy	14	33	0·7
No sphincterotomy	2	9	
Pancreatic stent	6	12	0·54
No pancreatic stent	10	30	
Mean age (years)	44	51	0·06
Mean duration of pancreatitis (months)	15	42	0·08
Mean period of biliary stenting (months)	12	21	0·12

*Fisher's exact test

of biliary stenting did not differ significantly between the groups.

Sixteen (28 per cent) of the 58 patients had surgical procedures for persistent biliary stricture after a median stenting period of 8·5 (range 0·8–39) months. Indications for surgery were: frequent stent-related complications in nine patients, duodenal stenosis in two and pancreatic surgery for chronic pain in five with chronic pancreatitis. Choledochojejunostomy was performed in seven patients, hepaticojejunostomy in four, choledochoduodenostomy in two, choledochotomy and sphincteroplasty in one, and Whipple resection in two. Five of the 16 patients had additional pancreatic or gastrointestinal drainage procedures, including pancreaticojejunostomy in three and gastroenterostomy in two. Additionally, five patients underwent cholecystectomy. There were no deaths in hospital.

Postoperative complications occurred in six of the 16 patients who had biliary drainage alone (two) or a combined procedure (four). Two patients developed an intra-abdominal haematoma after operation, which was evacuated surgically. One patient required relaparotomy to control bleeding from the splenic artery. One patient with recurrent cholangitis was successfully treated with

Table 2 Results of biliary stenting for chronic pancreatitis

Reference	No. of patients	Type of stent	Relief of symptoms	Stent dysfunction	Stent removed	Median (range) follow-up (months)
Deviere *et al.*[18]	19	Polyethylene	19 (100)	8 (42)	3 (16)	14 (7–42)
Barthet *et al.*[20]	19	Polyethylene	19 (100)	2 (11)	3 (16)	18 (13–48)
Present study	58	Polyethylene	58 (100)	37 (64)	16 (28)	49 (0·1–134)
Deviere *et al.*[19]	20	Wallstent	20 (100)	2 (10)	—	33 (24–42)

Values in parentheses are percentages

antibiotics. One patient developed a wound abscess which was drained. One patient with liver cirrhosis had multiple complications. He had persistent jaundice as a result of biliary leakage, treated by endoscopic biliary stenting. He developed infected ascites and secondary pleural empyema, which was treated by external drainage, and he also had bleeding at the anastomosis treated by sclerotherapy. Postoperative relief of jaundice and cholestasis was achieved in the remaining 15 patients. These patients had no recurrent jaundice or cholestasis over a median follow-up of 45 (range 6–98) months after surgery.

Discussion

Accepted indications for drainage procedures in patients with biliary obstruction due to chronic pancreatitis are the presence of persistent jaundice and/or cholangitis. However, the role of drainage procedures in asymptomatic patients with an isolated increase in the level of alkaline phosphatase remains controversial. Some authors advocate a conservative approach with periodic liver function testing without therapeutic intervention[2,9,16,22–24]. Others support drainage procedures in these patients to prevent long-term complications as a result of persistent cholestasis, such as secondary biliary cirrhosis and recurrent cholangitis[4–7,25]. A conservative approach would seem appropriate in asymptomatic patients with biliary stricture and a normal or slightly raised alkaline phosphatase concentration. Stenting implies a risk of introducing bacteria into the biliary tree and subsequent sludge formation. On the other hand, biliary drainage procedures should be performed in patients with biliary obstruction and proximal dilatation of the CBD, who are jaundiced or have a markedly raised alkaline phosphatase level, because of the risk of long-term complications such as secondary biliary cirrhosis and recurrent cholangitis.

Jaundice may resolve spontaneously in 20–50 per cent of patients with biliary obstruction due to chronic pancreatitis[3–6,11,23]. In these cases biliary obstruction may be temporary due to pancreatic oedema or compressing pseudocysts during an exacerbation of pancreatitis. The jaundice will subside without therapeutic intervention[3–6,11,23]. However, spontaneous resolution of symptoms mostly occurs within 1 month after commencement of the symptoms and is unlikely afterwards[3–6,9,11,23,26].

Table 2 gives an overview of previous studies[18–20] of endoscopic biliary stent insertion (plastic or Wallstents), in combination with the results of the present study. Immediate relief of jaundice and cholangitis was achieved in all patients in all studies. Two previous studies[18,20] showed that plastic stents could be removed in only 16 per cent of the patients with permanent relief of symptoms. However, the total number of patients was only 19 in both studies and the mean follow-up was 14 and 18 months. In the present study with a longer follow-up, stents could be removed and were the definitive treatment in more than one-quarter of patients.

The definitive success rate of biliary stenting was higher in patients with isolated cholestasis than in those with jaundice, probably due to less severe stricture in the former group. Biliary stenting was less successful in older patients and those with longer duration of the pancreatitis, which may be explained by more advanced disease in these patients.

As shown in *Table 2*, plastic stent dysfunction remained a frequent long-term complication. Self-expandable metal stents were associated with fewer stent-related complications, as shown by the study of Deviere *et al.*[19]. Only two of the 20 patients had metal stent occlusion as a result of epithelial hyperplasia. However, the present authors are reluctant to insert self-expanding metal stents in patients with benign disease, as the normal mucosal layer in the biliary tract is completely destroyed by metal stent insertion and long-term results are not yet available. Also, these stents cannot be removed.

In previous studies, surgical intervention for biliary obstruction and chronic pancreatitis was associated with considerable morbidity (15–30 per cent) and mortality (0–7 per cent) rates[1,9,11–17]. In the present series, the postoperative morbidity rate was high (six of 16 patients), but there were no deaths. The results of surgery may be influenced by negative selection of patients: most were referred for surgery after failure of endoscopic drainage. Furthermore, seven patients had multiple surgical drainage procedures, which may have contributed to the postoperative morbidity. Early morbidity in patients who had biliary drainage alone occurred in only two of nine.

The authors realize that no controlled studies have been performed to compare endoscopic biliary stenting and surgical therapy for chronic pancreatitis. Yet, based on the present findings, the following recommendations can be made. A biliary stent should be inserted in symptomatic patients with biliary obstruction due to chronic pancreatitis, and left in place for 1–3 months. After this period the stent may be removed (in case of stricture regression), stenting may be continued for a prolonged period of time or surgical drainage may be required. If the stent can be removed, endoscopic therapy offers definitive treatment. Stenting is continued in patients with persistent stricture who have contraindications for surgery (poor general condition, advanced age, portal hypertension) or who refuse operation. Surgical drainage is still the treatment of choice in young patients with persistent stricture and a good general condition. Other indications for surgery are the presence of duodenal stenosis and the necessity for additional pancreatic surgery for chronic pain. Surgical drainage should be performed after a short period of preoperative stenting (6–12 months).

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British Journal of Surgery 1996, 83, 769–770

For debate

Can we safely delay or avoid prophylactic colectomy in familial adenomatous polyposis?

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The current position

Colorectal cancer can be prevented in most patients with familial adenomatous polyposis (FAP) if they are offered colectomy shortly after diagnosis (or in the case of children, before the age of 20). Without prophylactic surgery, the median age of death was 37 years, mostly as a result of large bowel cancer. With prophylactic colectomy and ileorectal anastomosis (IRA) life expectancy has been improved by about 30 years, the most frequent cause of death now being upper gastrointestinal cancer, followed thereafter equally by rectal cancer and desmoid disease[1]. This improvement in survival is probably due to earlier diagnosis and timely prophylactic surgery, both of which have resulted in a fall in the proportion of colorectal cancers found in resected specimens of screened patients from 66 per cent to around 5 per cent[2].

What are the surgical choices in 1996? Colectomy and IRA is a tried and trusted procedure with low morbidity and good function, but the rectum remains at risk of cancer, and this risk seems to be age related, rising rather steeply from about 8 per cent before the age of 50 years to around 30 per cent by the age of 60[3]. The alternative is to remove the entire colon and rectum and create an ileal pouch which is then anastomosed to the anus, a procedure known as restorative proctocolectomy or the pouch operation. At first glance this operation seems ideal for polyposis; all large bowel mucosa is removed which means that rectal cancer should no longer be a problem. However, in practice[4,5] pouch surgery has more complications than an IRA, function is possibly worse, and should there be technical problems at the time of pouch construction or afterwards, then a permanent ileostomy can sometimes be the only solution, a grim prospect for a teenager who at the time of the original surgery was quite well and had no bowel symptoms. Furthermore, although rectal cancer occurs in 30 per cent of patients after IRA by the age of 60 years, it kills only about one-quarter of them[3].

The case for delay

Patients are not keen to have surgery, particularly when they are still young and at school and have yet to establish themselves in life with further education, employment and relationships. If there were a treatment that might delay or even obviate the need for an operation then many young men and women would jump at the chance.

There is in fact a possible way forward: surgery might be delayed until later in life when the argument in favour of a pouch is strongest. To adopt such an approach it would be necessary to have some idea who was most at risk of cancer and who was at least risk, and preferably to have some way to make some or all of the polyps disappear pharmacologically, and to monitor the whole situation reliably and safely.

Prediction of cancer risk

From the genotype

The *APC* (adenomatous polyposis coli) gene is very large and consists of 15 exons. There is a region in exon 15 where many mutations occur, but mutations have been identified along the entire length of the gene. There are now a number of reports that have identified particular mutations as being statistically associated with either a high[6–8] or a low[9,10] risk of cancer, but variation still occurs within members of the same family and between families with the same mutation, so modifier genes or environmental factors must also be important. This means that in an individual patient it is not safe to be guided clinically by knowledge of the mutation.

From the phenotype

Clearly the phenotype is largely determined by the genotype, but there are some useful differences. First, the influence of modifying genes can be detected; and second, in practice mutation analysis can be long and arduous, availability in clinical practice is non-existent and, even where mutation analysis is available, it is not always possible to identify the offending mutation.

The most obvious phenotypic markers are the patient's age, sex and number of colonic polyps. Whatever the genotype or phenotype, cancer risk rises with age in untreated patients. Under the age of 20 years, only 1 or 2 per cent of affected, untreated patients died, but over the next 5 and 10 years 15 per cent and 40 per cent respectively of all untreated patients with polyposis had died[1].

Patients with large numbers of colorectal polyps have the highest cancer risk. Patients with a colonic polyp count in the surgical specimen of more than 1000 have twice the risk of cancer than those with a smaller number. Nevertheless, around 5 per cent of patients with low polyp counts, under the age of 20 years, will be found already to have cancer in the resected specimen[11].

Monitoring

None of this would matter very much if those already with cancer could be detected reliably and safely. In practice, it can be hard to identify a small carcinoma against a background of sometimes innumerable colorectal polyps. St Mark's has experience of three patients in whom this was the case: in the first two, preresectional colonoscopy failed to identify cancers found on pathological exami-

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Paper accepted 27 September 1995

nation; in the last, both colonoscopy and pathological examination failed to identify the mucosal origin of a carcinoma identified histologically in lymph nodes.

Colonoscopy is not without its own complications, including failure to visualize the entire length of the colon and inadvertent perforation. Two patients from the St Mark's Registry suffered iatrogenic colonic perforation at monitoring colonoscopies (performed elsewhere) after polyposis had been diagnosed; one then developed a desmoid tumour and has a surgically irresectable colon still *in situ*[12].

Pharmacological treatments

Manipulation of cell proliferation can lead to polyp regression. Added vitamin C[13], dietary fibre[14] and calcium[15,16] have all been tried with only limited success, but the use of the non-steroidal anti-inflammatory drug (NSAID) sulindac has been shown to reduce colorectal polyp counts[17–19]. Unfortunately, reducing polyp counts does not necessarily equate with abolishing cancer risk, and cancer may arise in patients treated with sulindac[20,21].

Conclusion

In 1985 Narisawa *et al.*[22] wrote 'Right hemicolectomy followed by treatment with those drugs [NSAIDs] would prevent tumorigenesis in a much longer retained segment of the large bowel in patients with polyposis coli'; in 1990 Friend[17] wrote 'Nonetheless, physicians and informed patients may choose to try sulindac instead of surgery'; and in 1993 Evans and colleagues[23] wrote (on the basis of an untreated patient with polyposis) that they had disproved 'the oft quoted tenet that it is inevitable that someone with FAP will develop a bowel cancer'. This last patient subsequently went on to develop two colonic cancers.

Large bowel surgery in patients with polyposis should be prophylactic; cancer should be prevented rather than awaited expectantly and treated. Limited surgery has had astonishing success in cancer prevention and should not lightly give way to newer assessments of risk coupled to the selective application of alternative therapies. For those seeking to test new treatments, patients who have had colectomy with an IRA present an obvious avenue for investigation.

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British Journal of Surgery 1996, 83, 771–775

Topical glyceryl trinitrate in the treatment of chronic anal fissure

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The aetiology of anal fissure is unclear, but there is an association with high maximum resting pressure (MRP). Internal sphincterotomy reduces MRP and heals fissure through an increase in local blood supply. Glyceryl trinitrate (GTN) is a nitric oxide donor which contributes to internal anal sphincter relaxation via a non-adrenergic non-cholinergic pathway. GTN ointment was applied topically in different concentrations to the anal margin in patients with chronic anal fissure to monitor its effect primarily on MRP and secondarily on fissure healing. Nineteen patients with chronic anal fissure were treated with ointment containing increasing concentrations of GTN (0·2–0·8 per cent) to produce a reduction in MRP of greater than 25 per cent. The actual dose of GTN varied as no standard delivery system has been developed, but a 'typical amount' of GTN ointment weighed about 200 mg. In 15 of 19 patients, a concentration greater than 0·2 per cent was required to lower the MRP by at least 25 per cent. The minimum concentration of GTN that reduced the resting pressure by at least 25 per cent was prescribed and local application was carried out by the patient twice daily for 6 weeks. At 6 weeks, nine patients had healed, six required sphincterotomy and four were lost to follow-up. Eight of the nine patients with healed fistula required a GTN concentration of 0·3 per cent or more. Sixteen patients were resistant to the usually effective dose of 0·2 per cent GTN. In three there was tachyphylaxis and the duration of action of GTN was less than the 12 h described previously in control patients. Two patients did not fulfil the study because of headache.

The aetiology of anal fissure is unknown but patients tend to have a high anal maximum resting pressure (MRP)[1–4] which if reduced leads to fissure healing[2] and increased blood flow to the fissure ulcer[5]. Anal dilatation and lateral internal sphincterotomy lower the MRP and heal the fissure in most cases but with the complication of minor incontinence in up to 30 per cent of cases[1,3,6–10].

There is evidence that nitric oxide is involved as the inhibitory neurotransmitter to the human internal anal sphincter[11,12]. Glyceryl trinitrate (GTN) is an organic nitrate and donates nitric oxide. Topical GTN ointment has been shown to lower the MRP in asymptomatic controls and in patients with a variety of anal conditions[13]. Nitric oxide binds to the Fe^{2+} moiety of the heme molecule of guanylate cyclase in the smooth muscle cell cytoplasm and increases levels of the secondary messenger guanosine 3′,5′-cyclic monophosphate (cGMP)[14]. It is possible that nitric oxide produces relaxation of the smooth muscle cell via an alteration to potassium-activated channels in the cell membrane producing hyperpolarization; this may be through at least one route that involves cGMP[15]. Although other drugs are known to be direct or indirect nitric oxide donors, GTN was used as it is readily available, is absorbed transcutaneously and has been extensively investigated in this centre. Headaches are a common side-effect of GTN use; syncope and other side-effects are also possible[16].

Previous experience from this centre in control patients has shown that the reduction in MRP is 27 per cent and side-effects are minimized when 0·2 per cent GTN is applied to the anal margin[13]. An initial study by Kennedy *et al.*[17] using topical GTN to lower MRP in patients with anal fissure has, however, shown a healing rate only marginally better than that after conservative treatment.

Gorfine[18] used GTN in a heterogenous group of 15 patients with anal 'ulcers' and fissures of 2 days' to 2 years' duration. A dose of 500–1000 mg of 0·5 per cent topical GTN relieved pain but there was no indication as to why this dose was selected and anal manometry was not performed. The author concluded that '...it seems highly probable that the pain relief... was caused by nitric oxide-mediated relaxation of the IAS [internal anal sphincter]'.

There are three possible reasons for the failure of topical GTN to produce healing of a chronic anal fissure: a raised threshold to the relaxant action of topical GTN on the internal anal sphincter in patients with fissure compared with asymptomatic controls, a shorter than expected duration of action, and the development of tachyphylaxis (a previously effective dose becoming ineffective with time).

This study aimed to find an appropriate concentration of GTN that lowered MRP in the individual patient with fissure; and to determine its effectiveness in curing anal fissure.

Patients and methods

Outpatients presenting with chronic anal fissure were included in the study. Consecutive patients were accrued by a single researcher who was not blinded. Patients with Crohn's disease, women who might have been pregnant or who were considering pregnancy, and patients with ischaemic heart disease were excluded. Anal manometry was performed before and during treatment with GTN ointment. Ethical permission was obtained from the district ethics committee.

Definition of chronic anal fissure

Chronic anal fissure was taken to be an anal fissure in an outpatient who gave a history of anal pain on defaecation for at least 2 months. Some also experienced bleeding on defaecation, others a sentinel tag and/or an anal papilla, but these signs or symptoms were not considered necessary for inclusion in the study.

Glyceryl trinitrate

Preparation. Test ointments were prepared in the hospital pharmacy. Percutol (2 per cent GTN ointment; Cusi, Haslemere,

Paper accepted 23 August 1995

UK) was diluted in yellow soft paraffin to produce preparations of 0·2, 0·3, 0·4, 0·6 and 0·8 per cent GTN. Yellow soft paraffin is compatible with 2 per cent Percutol and was therefore used as the agent for dilution. Preparations were kept in a cool place in an opaque glass container with a screw top lid and discarded 4 weeks after formulation.

Dose. Like all other reported studies of the use of GTN[2,17,18] or isosorbide dinitrate[19] to treat anal conditions, there is no standard dose delivery system currently available. As with use of other ointments in the treatment of anal conditions, the amount used is variable, although in this study all patients appeared to follow instructions to use an amount that could be readily rubbed into the anal margin without creating a messy excess. This 'typical dose' was about 200 mg.

The amount of GTN absorbed was not measured but the paucity of side-effects of headache indicated minimal systemic absorption.

Assessment of healing

Patients were asked about the presence or absence of pain and bleeding on defaecation at each visit. Following surgical sphincterotomy, pain disappears before complete healing of the fissure, which may take several weeks. Therefore if there was no pain or bleeding on defaecation and there was evidence of complete or partial healing of the fissure with re-epithelialization, the treatment was deemed a success. However, this study was not primarily aimed at healing the fissure but at assessing the relative resistance of patients with fissure to the effect of GTN on MRP.

First visit

Anal manometry was performed using a 4-mm water-filled microballoon connected to a transducer and chart recorder. The catheter was inserted with a lubricant gel containing chlorhexidine but without local anaesthetic. After careful and thorough explanation of the test, all patients tolerated the microballoon well.

MRP was identified using a station pull-through technique and the catheter taped to the buttock leaving the balloon in the anal canal at that level. A steady resting pressure was allowed to develop over the next 12 min and its value recorded. Previous experience has shown that 12 min is sufficient for patients to attain a steady MRP.

GTN ointment (0·2 per cent) was applied circumferentially to the anal margin and gently rubbed in a clockwise direction for 5–8 s with the gloved index finger of the researcher. The ointment was not applied intra-anally. After a further 12 min, if a steady state had been reached, the MRP was recorded. If the pressure had not fallen by 25 per cent and the patient had not developed any side-effects, excess ointment was wiped away from the anal margin and the next concentration of GTN applied.

The same period of stabilization was permitted at each concentration and the procedure was repeated up to a concentration of 0·8 per cent GTN or until the resting pressure had fallen by 25 per cent of the original value. The minimum concentration of GTN ointment that lowered the MRP by at least 25 per cent was prescribed and the patient was instructed to use the ointment twice a day for 6 weeks. The patient was then reviewed at the second visit after 3 weeks.

Patients were questioned about compliance at each visit but no formal diary was maintained.

Second visit

Patients were asked to use the ointment on the morning of the test. Manometry was performed as at the first visit. The MRP after a 12-min stabilization period and the response of the MRP to a repeated application of the concentration of GTN ointment originally prescribed after 12 min were recorded. If this concentration now failed to lower the MRP, higher concentrations were applied. The development of tolerance to GTN (tachyphylaxis) and the duration of action of GTN could be inferred from these MRP measurements. Patients were specifically asked about headaches during treatment. They were then asked to apply GTN ointment for a further 3 weeks.

Final visit

At the end of 6 weeks the patient returned to the referring clinician for assessment of fissure healing.

Results

An overview of the results is given in *Fig. 1*.

Patient characteristics

The mean age was 44 (median 41, range 27–76) years; there were 13 men and six women. All had a posterior fissure. One woman subsequently developed an anterior fissure during treatment.

Pretreatment anal manometry

The mean MRP in 13 men was 155 (median 140, range 100–280) cmH_2O and that in six women 120 (median 123, range 70–170) cmH_2O.

First visit

MRP after topical application of 0·2 per cent GTN ointment in patients with anal fissure is shown in *Fig. 2*. There was a significant overall reduction ($P = 0{\cdot}007$, Wilcoxon paired test) but this resulted from large reductions in a few patients. A reduction of 25 per cent or more occurred in only three of the 19 patients. One patient developed headache despite a fall in MRP of only 16 per cent and withdrew from the study.

Of the remaining 15, a fall of 25 per cent was eventually achieved at a higher concentration in all but one who did not respond to 0·8 per cent GTN. He was referred immediately for sphincterotomy. Another patient did not return for subsequent visits. Sixteen patients therefore remained in the study.

Second visit

Of the 16 patients, 15 returned for the second visit. Six were symptom-free and the fissure had healed with ointment containing 0·2 per cent (one patient), 0·3 per cent (four) and 0·4 per cent (one) GTN. Nine still had a symptomatic fissure. Of these, two had stopped treatment and were referred for sphincterotomy after declining repeat anal manometry. The remaining seven had repeat manometry performed less than 8 h after application of GTN ointment (*Fig. 3*).

The percentage fall in MRP during the first and second visits of these seven patients is given in *Table 1*. Patients 1 and 2 showed evidence of tachyphylaxis and the previously effective dose of GTN ointment produced no reduction in MRP. The results for patients 3 and 4 suggest a duration of action of the GTN ointment of less than 8 h. Repeated application of GTN ointment reduced the MRP by 50 and 83 per cent respectively. In the remaining four patients, there was evidence of both tachyphylaxis and short duration of action.

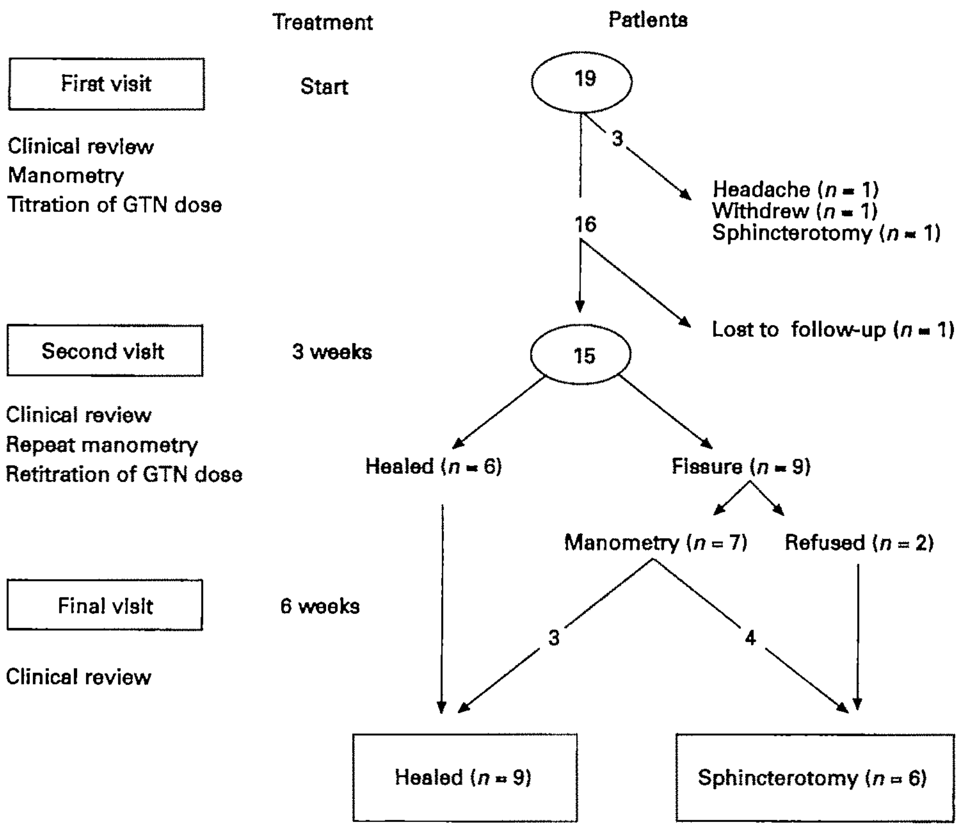

Fig. 1 Flow chart of glyceryl trinitrate (GTN) treatment in 19 patients over 6 weeks

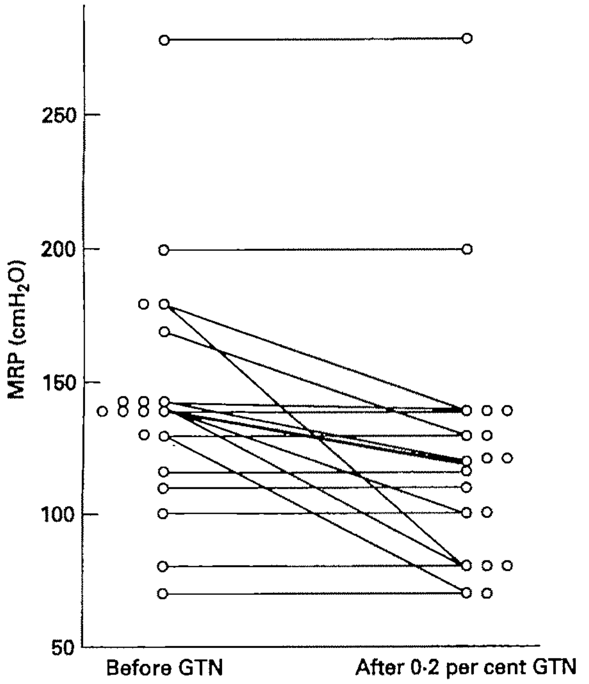

Fig. 2 Maximum resting pressure (MRP) in 19 patients before and after application of 0·2 per cent glyceryl trinitrate (GTN) ointment

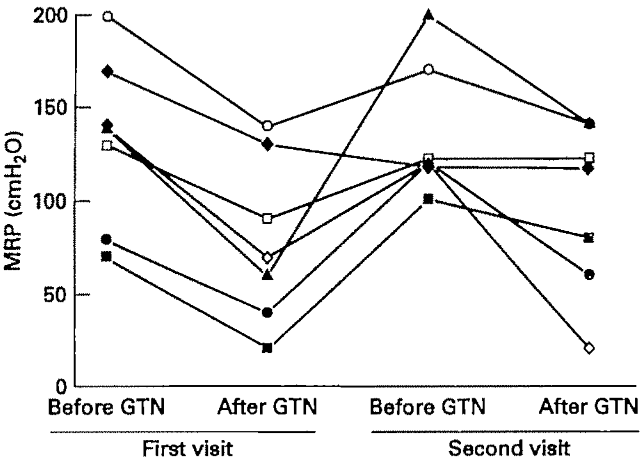

Fig. 3 Effect of glyceryl trinitrate (GTN) on maximum resting pressure (MRP) at the first and second visit in seven patients with persisting fissure. In these seven patients there was no significant difference between the MRP after GTN administration at the first and follow-up manometry assessments ($P = 0{\cdot}25$, Wilcoxon paired test)

Final visit

The fissure had healed in nine of the 13 patients remaining in the study. Four patients without fissure healing were referred for sphincterotomy. Of the nine patients whose fissure healed with GTN treatment, only

Table 1 Tachyphylaxis and duration of action of glyceryl trinitrate ointment as the possible cause of failure to heal seven patients

Patient no.	Percentage reduction in MRP after GTN ointment		Possible cause of failure
	First visit	Second visit	
1	25	0	Tachyphylaxis
2	28	0	Tachyphylaxis
3	50	50	Duration
4	50	83	Duration
5	71	20	Tachyphylaxis/duration
6	30	18	Tachyphylaxis/duration
7	57	30	Tachyphylaxis/duration

GTN, glyceryl trinitrate; MRP, maximum resting pressure

one healed with 0·2 per cent GTN ointment while five required 0·3 per cent, one 0·4 per cent and two 0·8 per cent GTN.

It was not possible to predict healing from the initial manometric response to GTN ointment.

Discussion

Surgical sphincterotomy is an excellent procedure for the long-term cure of chronic anal fissure. It probably works by reducing resting anal pressure (by as much as 50 per cent)[4,20–22]. There is evidence from laser Doppler studies that this may lead to improved perfusion of the pecten which might then facilitate healing of what are now known to be relatively ischaemic ulcers[1,23]. Further studies are required to confirm this.

As most fissures come and go an initial non-operative approach has been advocated by some[24,25]. Topical GTN, by producing a reversible 'chemical sphincterotomy', might increase the success of medical treatment. In a single-blind placebo-controlled trial Loder *et al.*[13] showed that 0·2 per cent GTN applied to the anal margin of patients with a variety of anal disorders reduced mean resting pressure by an average of 27 per cent. Another single-blind randomized placebo-controlled study in 42 patients with anal fissure showed a mean reduction in resting pressure of only 14 per cent but healing in 46 per cent within several weeks[17]. A further study that reported almost universal success with 0·5 per cent GTN did not use anal manometry to show the effects of this agent on MRP[18].

The present study had an overall success rate of 47 per cent (nine of 19 patients), compatible with results of others using GTN to lower MRP in patients with fissure[17]. It has also demonstrated some possible reasons for the high failure rate. First, the patients in the present study were relatively resistant to topical GTN. Only three showed a significant fall in MRP (more than 25 per cent) at a dose of 0·2 per cent GTN. This was a much lower proportion than that reported by Loder *et al.*[13]. In the latter study only one of 30 patients had an anal fissure. It is possible, therefore, that the pathogenesis of anal fissure is related in part to an insensitivity of the internal sphincter to endogenous nitric oxide.

Second, the duration of action of GTN ointment was less than the 12 h reported in two control patients[13]. The actual duration of action could not be determined in the present study but appeared to be less than 8 h in five of the seven patients in whom the fissure failed to heal. Further work on the dose–response relationship and the duration of action of GTN ointment is required. Where patients received more than one dose of different concentrations of GTN at a single session, it is possible that they effectively received a cumulative dose of GTN. However, it would not have been practical to ask the patients to return the following day if they failed at a particular concentration. In some cases, this may have meant patients returning on several consecutive days.

Third, five patients demonstrated an acquired tolerance to GTN. Tachyphylaxis is well recognized by physicians using nitric oxide donors for angina pectoris[26]. Tolerance is thought to result from a depletion of sulfhydryl groups which are necessary for biotransformation of organic nitrates to nitric oxide[27,28]. It may be possible to treat anal fissure with nitric oxide donors that do not rely on sulfhydryl groups and therefore are not subject to tachyphylaxis.

Before conducting a meaningful randomized trial of GTN *versus* placebo in patients with fissure, knowledge of the effective dose of GTN, appropriate frequency and duration of application and dose increments necessary to counter the effects of tachyphylaxis is required. Until these difficulties with GTN are overcome, the ad hoc use of an arbitrary concentration of GTN in an outpatients department without the use of manometry has little to recommend it.

Acknowledgements

S.J.W. is supported by the Robert Luff Foundation. The assistance of the Pharmacy Department of St Mark's Hospital in preparing the ointments is acknowledged.

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British Journal of Surgery 1996, 83, 776–777

Use of glyceryl trinitrate ointment in the treatment of anal fissure

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Anal fissure is often treated surgically by sphincterotomy. There is growing concern over the effects of this procedure on continence. Nitric oxide donors such as glyceryl trinitrate are thought to cause a reversible 'chemical sphincterotomy', capable of healing the fissure. Twenty-one consecutive patients with chronic anal fissure (13 women, mean age 36 years) were treated for 4–6 weeks with 0·2 per cent glyceryl trinitrate ointment applied to the fissure twice daily. Maximum anal resting pressure (MARP) was measured before and after application of the ointment at the first visit. There were 16 posterior and five anterior fissures. Mean(s.d.) MARP fell from 118·7(45·0) to 70·3(34·1) cmH$_2$O over 20 min after application of the ointment ($P < 0·001$). Healing was complete in 11 patients at 4 weeks and in 18 at 6 weeks. The fissure recurred in four patients after cessation of treatment; three were successfully treated by further glyceryl trinitrate. Mild headache occurred in four patients. Anal fissure can be successfully treated with 0·2 per cent glyceryl trinitrate ointment applied topically.

Anal fissure is a linear ulcer occurring in the distal anal canal. It is characterized by pain on defaecation, rectal bleeding and spasm of the anus. The aetiology of anal fissure is contentious, commonly thought to be related to constipation. Another recent theory is that anal fissure may be due to ischaemia of the posterior commissure of the anal canal, exacerbated by hypertonicity of the internal anal sphincter (IAS)[1,2]. Surgical treatments for fissure overcome this sphincter spasm by forcible anal dilatation or internal sphincterotomy. Both of these procedures are associated with short- and long-term impairment of continence in a variable proportion of patients[3–5]. In view of the growing concern over sphincter injury in women, a non-surgical method of reducing anal pressure may be appropriate[6].

Nitric oxide has recently been shown to be an important inhibitory neurotransmitter in the IAS[7,8]. Organic nitrates are degraded by cellular metabolism, releasing nitric oxide[9]. Glyceryl trinitrate ointment applied to the anus causes a fall in maximum anal resting pressure (MARP) amounting to a reversible 'chemical sphincterotomy'[10]. This study addresses the hypothesis that topical glyceryl trinitrate ointment may be a useful alternative to surgery for chronic anal fissure.

Patients and methods

Two per cent glyceryl trinitrate ointment (Percutol; Dominion Pharma, Haslemere, UK) was diluted 1:5 or 1:10 with white soft paraffin to give final concentrations of 0·2 and 0·4 per cent. Initially, one of these was applied to the anoderm of six normal volunteers to assess the severity and duration of headaches reported in a previous study[10].

Following this, 21 consecutive patients (13 women, mean(s.d.) age 36·3(9·8) years) who attended surgical outpatients with chronic anal fissure were recruited for the study. The study protocol was approved by the ethics committee of University Hospital, Nottingham, and informed consent was obtained from each patient.

On the first visit anal manometry was performed with a constantly perfused side-hole catheter. When the catheter had been in position for 20 min and a steady state had been reached, 0·5 g 0·2 per cent glyceryl trinitrate cream was applied to the lower anal canal. Manometry was continued for a further 40 min. MARP was recorded at steady state before and after application of the ointment. The patient was then given a supply of glyceryl trinitrate ointment and instructed on the dose (0·5 g) and method of application. The ointment was applied to the lower anal canal twice daily. No specific instruction regarding dietary modification was given, nor were sitz baths employed. The patients were reviewed at 2-weekly intervals. At each review patients were assessed for side-effects and the amount of pain experienced on defaecation. The anus was examined visually to assess healing of the fissure.

Results

Two normal volunteers receiving 0·4 per cent glyceryl trinitrate ointment experienced severe headache, lasting for 3 and 12 h. One of these also experienced slight dizziness for the duration of the headache. Four volunteers reported no adverse effects after application of 0·2 per cent glyceryl trinitrate ointment. No further use of 0·4 per cent ointment was made in the study.

In the patients with anal fissure, symptoms had been present for a mean of 25 (range 6–96) months and all had appearances of chronicity (induration, skin tag or visible IAS fibres). There were 16 posterior and five anterior fissures. Three had developed during pregnancy and one patient had Crohn's disease. Previous surgery had been performed for fissure in three patients; all had undergone internal lateral sphincterotomy and in two patients one or more anal stretches had also been performed.

Mean(s.d.) MARP fell from 118·7(45·0) to 70·3(34·1) cmH$_2$O 20 min after application of the ointment ($P < 0·001$, Student's paired t test) (*Fig. 1*). Healing of the fissure was complete in 11 patients at 4 weeks and in 18 at 6 weeks. All three patients with recurrent fissure after previous surgery healed with glyceryl trinitrate ointment.

Three patients had little or no fall in MARP after the application of the ointment, including the patient with Crohn's disease; these fissures did not heal.

In the 18 patients whose fissures healed, all reported that pain on defaecation had disappeared by the first review at 2 weeks. Mild headache occurred in four patients. Recurrence was seen in four patients whose fissures initially healed after 4 weeks' treatment with glyceryl trinitrate. Three of these recurrences were successfully treated by a further course of the ointment.

Paper accepted 25 September 1995

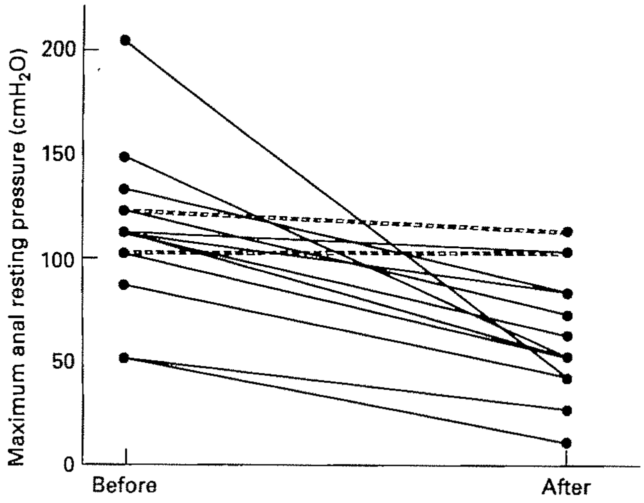

Fig. 1 Maximum anal resting pressure before and 20 min after application of 0·2 per cent glyceryl trinitrate ointment. Dotted lines indicate patients whose fissures were not healed by 6 weeks

Despite a significant reduction in MARP no patient complained of impaired continence during treatment with glyceryl trinitrate ointment.

Discussion

This study demonstrates that 0·2 per cent glyceryl trinitrate ointment applied topically to the lower anal canal significantly reduces MARP in most patients with anal fissure. In common with surgical sphincterotomy, 'chemical sphincterotomy' is associated with rapid relief of pain and leads to healing of the majority of chronic fissures by 6 weeks. In contrast with surgical sphincterotomy, 'chemical sphincterotomy' is reversible and is therefore unlikely to have long-term adverse effects on continence.

Nitric oxide has been shown to be a major inhibitory neurotransmitter of the IAS[7,8]. Various donors of nitric oxide have been used as topical applications with success in the treatment of anal fissure[10–12]. Schouten *et al.*[11] demonstrated that blood flow at the posterior commissure increased and MARP fell after the application of 1 per cent isosorbide dinitrate ointment. Healing of chronic fissure was seen in 67 per cent of patients at 6 weeks. However, this preparation needs to be applied to the anoderm six times daily. Topical nitroglycerine has been used to relieve pain caused by acute fissure and thrombosed external haemorrhoids, the proposed mechanism being reduction in the associated hypertonicity of the internal sphincter[12].

Patients with chronic anal fissure may have a reduced sensitivity to topical glyceryl trinitrate ointment, and tachyphylaxis to nitric oxide may develop[13]. In the present study 0·2 per cent glyceryl trinitrate ointment caused a fall in MARP in all but three patients; none of the latter showed any sign of healing of the fissure by 6 weeks. A higher concentration of glyceryl trinitrate ointment may have produced a fall in MARP in these patients. However, 0·4 per cent glyceryl trinitrate ointment induced severe headache in normal subjects in this study. Patients whose fissure recurred when the treatment was stopped were successfully treated with a further course of 0·2 per cent glyceryl trinitrate ointment, suggesting that tachyphylaxis was not a problem in this series.

Patients with recurrent anal fissure despite surgical treatment present a therapeutic dilemma in that further surgery to the IAS may lead to incontinence. In the present study three patients who had recurrent fissure after surgery were successfully treated with glyceryl trinitrate.

The role of topical glyceryl trinitrate in the treatment of chronic anal fissure appears promising and warrants further investigation.

Acknowledgements

This work was supported by a grant from the Wellcome Foundation.

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British Journal of Surgery 1996, 83, 778–780

Severe complications of perianal sepsis in patients with human immunodeficiency virus

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Fifty human immunodeficiency virus (HIV)-infected patients with perianal sepsis were studied. Seven (14 per cent) had serious septic complications, four patients with severe necrotizing gangrene, and three with abscesses in the mediastinum, liver and brain respectively. CD4$^+$ lymphocyte counts were significantly lower in patients with severe septic complications as compared with those with uncomplicated perianal sepsis ($P < 0{\cdot}05$). In patients with HIV presenting with rare (metastatic) abscesses, perianal sepsis must always be kept in mind as a possible focus. Although HIV-infected patients have a limited life expectancy perianal fistulas and abscesses should be aggressively treated, because of the high risk of severe complications.

Anorectal disease occurs in 6 to 34 per cent of patients with human immunodeficiency virus (HIV) infection especially in male homosexual patients[1–12]. Intravenous drug abusers with the acquired immune deficiency syndrome have a much lower incidence (3 per cent) of anorectal disease[5,6]. The frequency and type of anorectal disease seem to be related to the stage of HIV disease[5–8]. The clinical presentation of perianal sepsis (fistulas, abscesses) in HIV-infected patients may differ from that in non-immunocompromised patients. Moreover, because of the immunodeficiency, the frequency of severe complications of perianal sepsis might be higher than expected. The present study analysed the clinical presentation of perianal sepsis in relation to the immune status of HIV-infected patients.

Patients and methods

The medical records of patients with HIV, treated between 1 January 1984 and 1 September 1994, were reviewed with particular attention to perianal sepsis. Records were studied to identify age, sex, immune status (CD4$^+$ lymphocyte count), culture, clinical diagnosis, course and postoperative survival. In the study period 1342 HIV-infected patients were treated; 395 of these patients (29 per cent) were considered by a surgeon. Fifty (4 per cent) patients were found to have perianal sepsis (mean age 39 years; 48 homosexual or bisexual men). These patients underwent 92 surgical procedures for perianal sepsis. Perianal sepsis in patients with HIV was defined as perianal infection associated with abscess and fistula. Patients with perianal sepsis were only included in the study if, at the time of treatment, the patient was known to be HIV-seropositive.

The CD4$^+$ lymphocyte count (normal value $460–1450 \times 10^6$/l) assessed within a maximum of 6 weeks before surgical treatment, was considered to be representative of the patient's immune status on the date of treatment. Recent preoperative CD4$^+$ lymphocyte counts were available before 68 of 92 operative procedures for perianal sepsis (74 per cent). These data were used to analyse the relation between the preoperative CD4$^+$ lymphocyte count and the development of septic complications.

The χ^2 test was used to test for differences between proportions. Postoperative survival time was calculated from the first operation until death or end of the study period. The postoperative survival curve was calculated using the Kaplan–Meier method; comparisons were performed with the log rank test. P less than 0·05 was considered significant.

Results

Clinical data

Patient characteristics and postoperative survival time of patients with perianal sepsis are shown in *Table 1*. Seven (14 per cent) of the 50 patients had serious septic complications, consisting of necrotizing gangrene (four) and metastatic abscesses (three).

Necrotizing gangrene. All four patients with severe necrotizing gangrene, aged between 34 and 41 years, were male and homosexual. Symptoms included severe anal pain, purulent discharge, fever (39–40°C), anorexia and general discomfort. Previous treatment for perianal fistula had occurred in all four patients. On examination, gangrenous penis and scrotum, fistula (two patients), abscess (one patient) and extensive anorectal ulceration with infiltrate were encountered. In one patient a necrotizing perineum was found without a clear fistula tract or perianal abscess. However, as this patient frequently presented with recurrent perianal fistula it was considered that the necrotizing gangrene originated from these fistulas. Cultures revealed mixed flora in all patients (among others *Klebsiella pneumoniae*, haemolytic *Streptococcus* group C, *Streptococcus milleri*, *Proteus mirabilis* and various anaerobes). On the day of admission all patients underwent extensive necrosectomy and

Table 1 Patient characteristics and postoperative survival time of patients with perianal sepsis with or without complications

	Severe complication ($n=7$)	No complications ($n=43$)
Sex ratio (m : f)	7 : 0	42 : 1
Mean (range) age (years)	40 (34–46)	39 (31–56)
Median (range) survival time (years)	2·3 (0·1–3·0)*	3·3 (1·6–3·8)*

*$P = 0{\cdot}28$

Paper accepted 8 August 1995

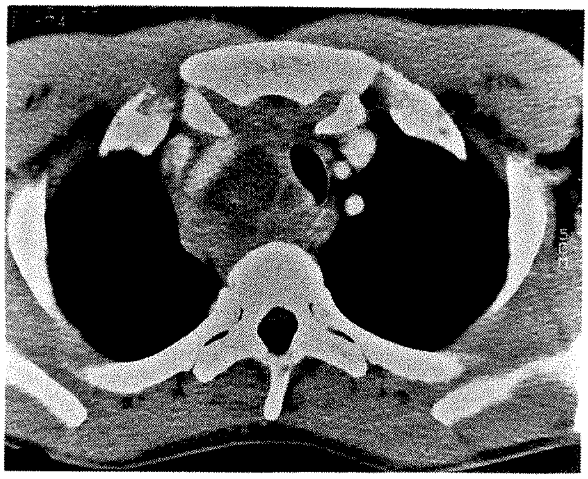

Fig. 1 Computed tomography of the chest showing metastatic abscess in the superior mediastinum in a patient with asymptomatic perianal fistula

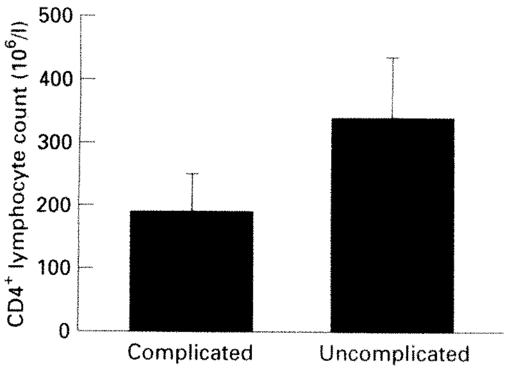

Fig. 2 Mean(s.e.m.) $CD4^+$ lymphocyte count ($\times 10^6$/l) of patients with perianal sepsis with or without complications. $P < 0{\cdot}05$

received broad-spectrum antibiotic treatment. Subsequently, antibiotics were modified according to the results of bacterial cultures. In three patients necrotizing fasciitis was progressive and, therefore, a diverting colostomy was performed. In one of these three patients the postoperative course was complicated by wound dehiscence, which was resutured primarily. In the fourth patient a diverting stoma had already been constructed earlier because of anorectal ulceration. In all patients multiple necrosectomies (between two and six per patient) followed every 1–3 days. The wounds healed 3–7 weeks later. Hyperbaric oxygen treatment was added in two patients as necrotizing fasciitis was rapidly progressive. The four patients were discharged from hospital 6–9 weeks after admission.

Metastatic abscesses. Three patients presented primarily with abscesses in the mediastinum, liver or brain respectively. They were all homosexual men. Symptoms consisted of severe chest pain (mediastinal abscess), upper right abdominal pain (liver abscess) or meningeal tenderness and aphasia (brain abscess). No patient had perianal pain and/or spontaneous discharge. History included previous treatment of perianal abscesses in one patient and fistula in two patients. On examination intermittent fever (38–39·5°C) and perianal fistula were encountered. The liver abscess, located in segment eight of the liver, was surgically drained. The brain abscess was located frontotemporally on the left side of the brain and evacuated at craniotomy. The mediastinal abscess was radiologically drained three times under computed tomography (CT) guidance (*Fig. 1*). All three patients were immediately treated with broad-spectrum antibiotics, modified according to the results of the bacterial cultures. Bacteriological cultures of the three abscesses were identical to those found in the perianal focus (among others *Kl. pneumoniae*, haemolytic *Streptococcus* and various anaerobes). Further examination of the perianal region was carried out under general anaesthesia and, after the initial treatment of the metastatic abscess, the residual perianal abscess was drained in one patient and the residual perianal fistula laid open in two patients. Wound healing disorders did not occur in these three patients. All patients were discharged 4–10 weeks after admission.

Immune status and septic complications

Immune status was significantly more disturbed in patients with septic complications as compared with those with uncomplicated perianal sepsis ($P < 0{\cdot}05$; *Fig. 2*).

Postoperative survival time

Twenty-eight of the 50 patients with perianal sepsis (56 per cent) died during the study period. There was no inhospital mortality after operative treatment for perianal sepsis. Median postoperative survival time of patients with complications was 2·3 years after surgery. For patients without complications median postoperative survival time was 3·3 years. The difference in postoperative survival time between groups did not reach statistical significance. Death was not related to perianal sepsis in any patient.

Discussion

In the present study, frequency of perianal fistula and abscess in patients with HIV was relatively high (4 per cent) in comparison with that in non-HIV-infected patients (1·6 per cent)[13]. Atypical presentation of perianal sepsis with severe septic complications (necrotizing gangrene and metastatic abscess) was encountered in 14 per cent of patients.

In four patients necrotizing gangrene (Fournier's gangrene) was diagnosed. This is a life-threatening synergistic necrotizing fasciitis, which involves the genital area, perineum and perianal region. It results in early septicaemia and carries a considerable mortality. The treatment consists of aggressive surgical debridement, systemic antibiotics and in most patients a temporary colostomy is required. One report stresses the importance of hyperbaric oxygen therapy in patients with necrotizing gangrene, but there is no conclusive evidence that the final outcome can be improved with this treatment[14,15]. The incidence of necrotizing gangrene in general surgical practice is very low[16-18]. Review of the literature revealed one such case in an HIV-infected patient[19]. During the development of necrotizing gangrene, two of the four patients also had asymptomatic fistula. Therefore, it is important that not only perianal abscesses are adequately drained, but also that perianal fistulas are treated effectively.

Metastatic abscesses were observed in three patients.

These abscesses are frequently reported as originating from infected puncture sites in HIV-infected intravenous drug abusers[20]. However, those derived from perianal sepsis have not been reported in HIV disease. The three patients in the present study represent unusual life-threatening complications of perianal sepsis. At the time of diagnosis of metastatic abscesses in these patients, asymptomatic fistulas were also found to be present. It is difficult to determine whether the metastatic abscesses originated from these asymptomatic fistulas or whether they developed during a previous period of purulent retention. In all three patients the metastatic abscesses were successfully drained, either by open surgical technique or CT-guided puncture. Surgical treatment of perianal sepsis in HIV-infected patients consisting of adequate drainage of perianal abscesses can probably prevent metastatic abscesses or necrotizing fasciitis. Fistulas are treated by fistulectomy or by laying them open electively. A conservative approach is not justified, because of the relatively high risk of serious complications, despite the risk of damaging an already weakened sphincter and causing diarrhoea.

Immune status, as measured by preoperative $CD4^+$ lymphocyte count in seven of 50 patients, showed a correlation with the septic complications of perianal sepsis. A low $CD4^+$ lymphocyte count is a significant risk factor for the development of septic complications. A precise description of wound healing in HIV-infected patients with anorectal disease (including perianal sepsis) has been published elsewhere[21]. In that study low $CD4^+$ lymphocyte counts were shown to be a risk factor for the development of disturbed wound healing in these patients[21].

In conclusion, perianal sepsis with severe septic complications, such as necrotizing gangrene and metastatic abscesses, can be relatively common in HIV-infected patients and may present with unusual complications which are extremely rare in patients not infected with HIV. When HIV-infected patients present with rare metastatic abscesses, perianal sepsis must be considered as a possible focus. These complications are associated with a decreased immune status. Perianal fistulas in such patients should be laid open or treated by fistulectomy. Perianal abscesses require adequate drainage, in order to avoid necrotizing gangrene and metastatic abscesses. There seems to be little place for a conservative approach in HIV-infected patients despite a very limited life expectancy.

Acknowledgements

The authors are indebted to J. Oosting (Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, The Netherlands) for assistance with statistical analysis.

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British Journal of Surgery 1996, 83, 781–785

Prognostic significance of radial margins of clearance in rectal cancer

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A retrospective review of 325 patients was undertaken to analyse whether involvement of the radial resection margin (RRM) could predict locally recurrent disease or distant metastases in patients who had curative surgery for rectal or rectosigmoid cancer. Information on the RRM was available in 253 patients. The RRM was involved in 31 (12 per cent). Nine of these 31 patients developed local recurrence (29 per cent), while only 17 local recurrences were diagnosed in 217 patients (8 per cent) without involvement of the RRM ($P<0{\cdot}01$). At 2 years the overall local recurrence rate was 10 per cent. Distant metastases were diagnosed in 46 patients (18 per cent) and RRM involvement was identified as a prognostic factor depending on lymph node involvement (N stage) ($P=0{\cdot}02$). Local recurrence and some distant metastases result from microscopically incomplete resection. Assessment of the radial depth of tumour invasion by careful histological examination of the specimen may be used for selection of patients for adjuvant radiotherapy and/or chemotherapy.

After curative resection of rectal or rectosigmoid cancer the overall local recurrence rate is variable, ranging from 0 to 67 per cent[1–4]. Knowledge of the predictive factors for local failure is important and might be used to guide selection of patients for adjuvant therapy. Some of these predictive factors are well known, such as T stage[5], N stage[5], number and site of involved lymph nodes[1,6], Dukes classification[4,7,8], site of the primary tumour[9], type of surgery[9], histological tumour type and grade[4,8,10], tumour extension beyond the bowel wall[4] and clinical features such as tumour mobility, obstruction or perforation[8].

It is possible that local failure occurs after incomplete removal of the tumour as established by microscopic examination. This often occurs at the radial aspect[11–14]. Conventionally only the proximal and distal margin involvement of the resected specimen is reported[9]. Quirke *et al.*[11] found a positive predictive value of 85 per cent for local recurrence when the lateral resection margin was involved in 52 patients who had curative operations for rectal cancer. This was recently confirmed in a report by Adam and colleagues[12].

The present authors started histological examination of the radial resection margin (RRM) in 1989 and the aim of this study was to analyse whether involvement of the RRM could predict locally recurrent disease and distant metastases.

Patients and methods

Data on a group of 325 patients treated curatively with either surgery alone or surgery with adjuvant radiotherapy for adenocarcinoma of the rectum or rectosigmoid were extracted from the database of the Cancer Registry, Comprehensive Cancer Centre Limburg (IKL)[15]. Patients who had metastases at initial investigation, identified by computed tomography (CT) or ultrasonography of the upper abdomen, or at the time of surgery, detected by palpation of the liver, were excluded. The resections were performed in the surgical departments of eight hospitals in the IKL area between January 1989 and January 1992. The eight hospitals consisted of one university hospital and several large and small district hospitals covering a region with a population of 850000, including urban and rural areas. Patients at high risk of local failure were selected for postoperative radiotherapy. Patients in this group had either peroperative tumour spillage or microscopically incomplete resection with respect to the cranial, caudal and radial margins.

The radial margin was examined according to the method described by Quirke and co-workers[11]. Briefly, the procedure entailed obtaining cross-sections of the resection specimen in the tumour region in slices 4 mm thick after inking the entire perirectal circumference to identify the RRM. The slice showing deepest tumour infiltration macroscopically was processed further for histological examination and evaluated as shown in *Fig. 1*. The radial margin was defined as involved or positive when the shortest distance between the site of deepest tumour infiltration and the surgical resection margin was less than 1 mm. After a consensus meeting, in which details of the examination procedure were discussed and agreed, specimens were handled and reported by the local pathologists of the participating hospitals. Nevertheless, 57 patients were treated in one hospital where the pathologist did not meet the consensus criteria; these patients were not eligible for further study. Of the remaining 268 patients, the pathology report did not mention the radial tumour-free margin in 15. Staging was performed according to the Union Internacional Contra la Cancrum tumour node metastasis (TNM) classification[5].

Rectal cancers were defined as those located within 15 cm of the anal verge by sigmoidoscopy, and rectosigmoid tumours

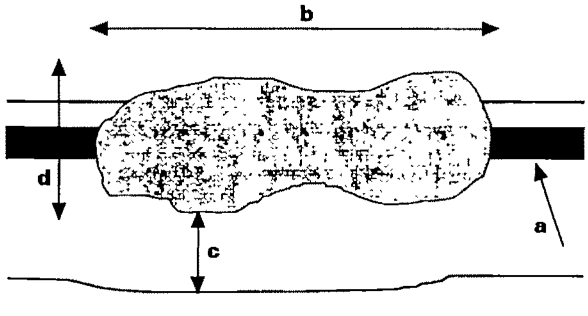

Fig. 1 Longitudinal section of tumour showing a muscularis propria, b maximal length, c radial resection margin and d maximal thickness. Measurements are in millimetres

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Paper accepted 13 September 1995

those within 15–25 cm. Patients were considered to have pelvic recurrence if there was a palpable mass by digital rectal examination, recurrence identified endoscopically or if the history suggested pelvic recurrence (e.g. bleeding, faecal incontinence, sciatic or perineal pain); this was confirmed by CT of the lower abdomen.

Metastases were usually diagnosed by a combination of clinical parameters (e.g. fatigue, anorexia, nausea, vomiting, weight loss), laboratory parameters (liver function tests and carcinoembryonic antigen level), and radiological evidence (ultrasonography and/or CT of the upper abdomen).

All patients were seen regularly for follow-up by the surgeon, and irradiated patients by both the surgeon and radiotherapist. Five patients (2 per cent) were lost to follow-up. Local control rates, occurrence of distant metastases and survival were reported after a minimum follow-up of 2 years. The median duration of follow-up was 29 months.

Statistical analysis

The Kaplan–Meier method was used to estimate survival and local control rates. The log rank test was used to test differences between curves in the univariate analysis. A multivariate analysis according to the Cox regression model was performed. For the analysis of contingency tables the χ^2 test was employed. Results have been quoted as statistically significant if the probability of chance occurrence was less than 5 per cent.

Results

A positive RRM (less than 1 mm) was found in 31 (12 per cent) of 253 specimens. In 222 patients this margin was not involved. There were 212 rectal and 40 rectosigmoid cancers. In one patient information on the exact location was not available. Some 161 patients (64 per cent) had a low anterior resection (LAR) and 80 (32 per cent) an abdominoperineal resection (APR). A few patients had a Hartmann's procedure, transanal resection or another procedure (5 per cent). Tumour stage was T_1 in 25 patients (10 per cent), T_2 in 76 (30 per cent), T_3 in 144 (57 per cent) and T_4 in seven (3 per cent). Lymph nodes were involved in 80 (31 per cent) patients (N_+) and clear in 167 (66 per cent) (N_0). In six patients information on N stage was not available. Seventy-six patients had metastatic disease, identified by CT or ultrasonography of the upper abdomen, and were excluded.

Seven patients received adjuvant chemotherapy (3 per cent), 28 (11 per cent) received postoperative radiotherapy and one patient a combination of chemotherapy and radiotherapy. In 18 patients (7 per cent) there was peroperative spillage of tumour cells; 12 of these received adjuvant radiotherapy. In 16 patients the reason for postoperative radiotherapy was a positive RRM. Eighteen patients who should have received radiotherapy to conform to the regional consensus did not because of old age and other concomitant circumstances.

The relationship between T stage, N stage, site of the primary tumour, type of surgery and RRM are shown in *Table 1*. A positive RRM was associated with increasing T stage and correlated with the type of surgery.

Local control

The overall local recurrence rate was 10·5 per cent (26 patients). The relationship between local control after 2 years and RRM, T stage, N stage, site of primary tumour, type of operation and adjuvant therapy is shown in *Table 1*. After 2 years the local control rate was 75 per cent when the RRM was involved *versus* 92 per cent when the RRM was free from tumour (*Fig. 2*).

A total of nine local recurrences was documented in 31 patients (29 per cent) with involvement of the RRM, while only 17 recurrences (8 per cent) were found in 217 patients with clear margins ($P<0{\cdot}01$). To test the

Table 1 Parameters related to radial resection margin involvement and influencing local control rate: univariate analysis

Parameter	No. of patients	No. with positive RRM*	χ^2	d.f.	P	Local control (%)†	χ^2	d.f.	P
RRM									
<1 mm	31					75 (67–83)	15·090	1	<0·01
>1 mm	217					92 (90–94)			
T stage									
T_1	25	1 (4)	9·107	1	<0·01	95 (92–98) ($T_{1/2}$)	3·379	1	0·07
T_2	76	3 (4)							
T_3	144	23 (16)				86 (83–89) ($T_{3/4}$)			
T_4	7	4 (57)							
T_x	1								
N stage									
N_0	167	17 (10)	2·808	1	0·09	91 (89–93)	0·468	1	0·50
N_+	80	12 (15)				86 (82–90)			
N_x	6	2 (33)							
Site									
Rectum	212	24 (11)	0·434	1	0·51	90 (88–92)	1·452	1	0·23
Rectosigmoid	40	6 (15)				85 (79–91)			
Surgery									
LAR	161	13 (8)	8·512	1	<0·01	91 (88–94)	1·481	1	0·22
APR	80	17 (21)				87 (83–91)			
Other	12	1 (8)							
Adjuvant therapy									
Radiotherapy only	28					81 (73–89)	8·231	3	0·04
Chemotherapy only	7					100 (3 at risk)			
None	212					90 (88–92)			

Values in parentheses are *percentages or †ranges. RRM, radial resection margin; LAR, low anterior resection; APR, abdominoperineal resection

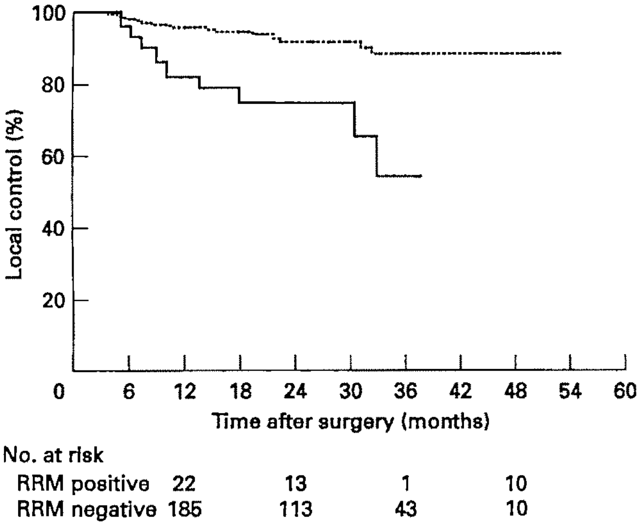

Fig. 2 Local control curves for patients with a positive (less than 1 mm; ———) or negative (------) radial resection margin (RRM) from the day of surgery

usefulness of involvement of the RRM as an indicator of increased risk of local recurrence, the sensitivity, specificity, positive and negative predictive values of this factor were calculated. These were 35, 90, 29 and 92 per cent respectively.

In the multivariate analysis involvement of the RRM ($P < 0{\cdot}01$) was identified as an independent prognostic factor for local control (*Table 2*).

Distant metastasis-free survival

Distant metastases were diagnosed in 46 patients (18 per cent). T stage and N stage were identified as prognostic factors for distant metastasis-free survival in the univariate analysis (*Table 3*), while in the multivariate analysis only the RRM was identified as an independent prognostic factor (*Table 4*). Because of this discrepancy between the univariate and multivariate analysis an interaction term between N stage and RRM, N stage and T stage and/or T stage and RRM was performed. The multivariate analysis was repeated after addition of these three interaction terms in the model (*Table 5*). An interaction term was present between N stage and RRM, and N stage and T stage. This suggested that the prognostic significance of both RRM and T stage depends on the lymph node status. In the case of negative lymph nodes (N_0) the relative risk of $T_{3/4}$ *versus* $T_{1/2}$ was 3·4, and that of a positive RRM *versus* a negative RRM was 1·4. In the case of positive lymph nodes (N_+) the relative risk of $T_{3/4}$ *versus* $T_{1/2}$ was 1·4 and that of a positive RRM *versus* a negative RRM was 2·0. These results suggest that the RRM is a risk factor for distant metastases only in lymph node-positive patients.

Survival

The calculated overall survival rate was 84 (95 per cent confidence interval 81–87) per cent. After 2 years of follow-up, 140 patients were still at risk and 34 had died (two during admission for primary treatment, 17 with distant metastases, two with locally recurrent disease, two with both distant metastases and local recurrence, and 11

Table 2 Multivariate analysis for local control

Variable	Regression coefficient	Standard error	*t*	*P*
RRM (RRM < 1 mm *versus* RRM > 1 mm)	1·3232	0·4144	3·1929	< 0·01
T stage ($T_{1/2}$ *versus* $T_{3/4}$)	0·3462	0·2607	1·3281	0·19
N stage (N_0 *versus* N_+)	0·0264	0·1412	0·1873	0·85
Site (rectum *versus* rectosigmoid)	0·3308	0·4984	0·6637	0·52

RRM, radial resection margin

Table 3 Univariate analysis of parameters influencing survival rates for patients with resected rectal or rectosigmoid cancer

Parameter	Distant metastasis-free survival (%)	χ^2	d.f.	*P*
RRM				
< 1 mm	70 (61–79)	1·627	1	0·20
> 1 mm	84 (81–87)			
T stage				
T_1–T_2	93 (90–96)	12·60	1	< 0·01
T_3–T_4	74 (70–78)			
N stage				
N_0	93 (91–95)	43·83	1	< 0·01
N_+	60 (54–66)			
Site				
Rectum	82 (79–85)	0·271	1	0·60
Rectosigmoid	80 (74–86)			
Surgery				
LAR	82 (79–85)	0·501	1	0·48
APR	80 (75–85)			

Values in parentheses are ranges. RRM, radial resection margin; LAR, low anterior resection; APR, abdominoperineal resection

Table 4 Multivariate analysis for distant metastasis-free survival

Variable	Regression coefficient	Standard error	*t*	*P*
RRM (RRM < 1 mm *versus* RRM > 1 mm)	0·6450	0·2321	2·7796	< 0·01
T stage ($T_{1/2}$ *versus* $T_{3/4}$)	0·2369	0·1733	1·3676	0·18
N stage (N_0 *versus* N_+)	0·1259	0·0893	1·4098	0·20

RRM, radial resection margin

Table 5 Multivariate analysis with interaction terms for distant metastasis-free survival

Variable	Regression coefficient	Standard error	*t*	*P*
RRM (RRM < 1 mm *versus* RRM > 1 mm)	0·3327	1·5630	0·2129	0·83
T stage ($T_{1/2}$ *versus* $T_{3/4}$)	1·2234	1·2071	1·0135	0·33
N stage (N_0 *versus* N_+)	4·1405	1·0669	3·8808	< 0·01
N stage × T stage	0·9759	0·2632	3·7085	< 0·01
N stage × RRM	0·3322	0·1417	2·3448	0·02
T stage × RRM	0·0317	0·5116	0·0620	0·95

RRM, radial resection margin

Table 6 Parameters influencing survival rates for patients with resected rectal or rectosigmoid cancer: univariate analysis

Parameter	Survival rate (%)	χ^2	d.f.	*P*
RRM				
<1 mm	85 (78–92)	0·757	1	0·38
>1 mm	84 (81–87)			
T stage				
T_1–T_2	93 (90–96)	10·293	1	$<0·01$
T_3–T_4	78 (74–82)			
N stage				
N_0	91 (88–94)	15·590	1	$<0·01$
N_+	71 (66–76)			
Site				
Rectum	84 (81–87)	3·929	1	0·05
Rectosigmoid	80 (73–87)			

Values in parentheses are ranges. RRM, radial resection margin

Table 7 Multivariate analysis for overall survival

Variable	Regression coefficient	Standard error	*t*	*P*
RRM (RRM < 1 mm *versus* RRM > 1 mm)	0·1822	0·2252	0·8088	0·42
T stage ($T_{1/2}$ *versus* $T_{3/4}$)	0·1906	0·1584	1·2035	0·23
N stage (N_0 *versus* N_+)	0·1756	0·0903	1·9441	0·05
Site (rectum *versus* rectosigmoid)	0·4388	0·3454	1·2706	0·22

RRM, radial resection margin

with no evidence of disease). The relationship between RRM, T stage, N stage and survival 2 years from the date of curative surgery can be seen in *Tables 6* and *7*. In multivariate analysis only N stage ($P = 0·05$) was related to overall survival.

Discussion

After 2 years the local recurrence rate was 10·5 per cent, which compares favourably with results reported in the literature[1–4]. The length of follow-up was relatively short (median 29 months); however, reports from the literature indicate that about 60–75 per cent of local recurrences occur within 2 years of surgical resection. These results show that attention to surgical technique is important.

Eighty patients (32 per cent) had an APR. This percentage is high for a modern series but the median distance from the anal verge to the lower part of the tumour was 6 cm. In patients who had a sphincter-sparing procedure this distance was 11·5 cm. Involvement of the RRM was substantially more frequent in the group that had APR. One reason for the low local recurrence rate in this series might be that other surgeons are more anxious to perform LAR while sacrificing local control. These results were obtained by surgeons with and without special interest in gastrointestinal surgery and by surgical trainees.

Excellent results were obtained by Heald and Ryall[16], who reported a local recurrence rate of 3·7 per cent at 5 years after complete excision of the mesorectum with the cancer. It was concluded that lymphatic spread of tumour in the mesorectum or mesosigmoid was a more significant factor for local recurrence than craniocaudal spread. Other studies have confirmed the importance of RRM involvement in relation to local recurrence and poor prognosis[12–14]. The reported incidence of RRM involvement varies from 20 to 25 per cent[12,13]. In the present series a positive RRM was seen in 12 per cent of patients. As expected, this was related to the depth of tumour penetration (T stage) and to the type of surgery. The latter relationship, although not significant, was reported by Quirke *et al.*[11], who found involvement of the RRM in 39 per cent of patients after APR and in 17 per cent after sphincter-sparing resection.

The positive predictive value of RRM involvement for local recurrence found in two other studies was 85 per cent[11] and 53 per cent[13] compared with 29 per cent in the present series. Since predictive values depend strongly on the prevalence of abnormality (i.e. local recurrence)[17], this relatively low predictive value may result from the low overall local recurrence rate in these patients (10·5 per cent). The local recurrence rate in the series of Quirke and colleagues[11] was 23 per cent. RRM involvement was identified as an independent prognostic factor related to local recurrence. A more careful examination of the RRM would improve prediction of local recurrence, and allow standardization of pathological reporting which would be beneficial for interpretation of (multicentre) trials of adjuvant radiotherapy.

In 18 patients there was peroperative tumour cell spillage. This might have been a direct consequence of the technical difficulty of tumour removal or an effect of the local radial invasion. Four of these 18 patients developed local recurrence, three of whom had received adjuvant radiotherapy.

No conclusions about the effect of postoperative radiotherapy can be drawn from this study but a reduction in local recurrence rate from 21 to 12 per cent has been reported in a prospective trial of 471 patients randomized to preoperative radiotherapy for all tumour stages or postoperative radiotherapy for high-risk groups (stage B_2, C_1, C_2)[18]. Patient selection for radiotherapy may be improved using transrectal ultrasonography or endorectal surface coil magnetic resonance imaging[19,20]. As the local recurrence rate in this study was only 10·5 per cent one might question the need for preoperative radiotherapy.

Other studies have found that local failures are more frequent when lymph nodes are involved[1,6], but in this series there was no relationship between N stage and local recurrence. At least in the medium term, N stage is a prognostic factor for distant metastases while the radial margin and T stage are prognostic factors interacting with nodal stage.

The ability to predict local recurrence of rectal or rectosigmoid cancer provides a rational basis for a trial of postoperative radiotherapy. By selecting patients with a positive RRM who are at high risk, such a trial would be statistically powerful by removing patients likely to be cured by surgery and avoiding radiotherapy in those with a low risk of local recurrence.

The RRM might be related to the development of distant metastases in node-positive patients but seems not to influence overall survival in the medium term.

Acknowledgements

The authors thank all members of the Gastrointestinal Study Group of the Comprehensive Cancer Centre Limburg for their support and for giving permission to report patients under their care, and Drs M. Pannebakker, P. Theunissen, J. Koudstaal, T. Ceelen, W. Kwee and A. Willig for histological analysis.

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British Journal of Surgery 1996, 83, 786–787

Short note

Colonic decompression without on-table irrigation for obstructing left-sided colorectal tumours

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The detrimental effects of massive fluid shift and the prolongation of operating time are often cited as reasons for hesitation in adopting 'intraoperative irrigation' for the treatment of left-sided colorectal obstruction[1]. Mechanical bowel preparation has been shown to be unnecessary for elective colorectal surgery[2]. Colonic decompression without intraoperative irrigation may therefore simplify operation in acute left-sided colorectal obstruction; complete bowel cleansing is unnecessary.

Patients and methods

Records of all patients with an acutely obstructed colorectal carcinoma at or distal to the splenic flexure who were treated with intraoperative decompression between April 1989 and December 1994 were studied retrospectively. Patients who underwent extended right hemicolectomy or total colectomy were excluded from the study, and only those with a radical left-sided colectomy were included. All patients underwent standard radical left hemicolectomy or anterior resection. Those admitted under the care of one consultant (F. S.-C.) underwent intraoperative bowel decompression without colonic irrigation (group 1), while those under either of the other two consultants (Y.H.H. and A.F.P.K.L.) had intraoperative bowel decompression and colonic irrigation (group 2).

In each patient a segment of colon proximal to the tumour was transected between clamps, and the proximal end was attached to an anaesthetic elephant tube leading to a bag to collect intestinal effluent. In patients who had intraoperative bowel decompression and colonic irrigation, a Foley catheter was then introduced via an appendicostomy. Orthograde colonic lavage was carried out with 0·5 per cent chlorhexidine solution following bowel decompression[3], until the effluent was clear. In patients who had intraoperative bowel decompression without colonic irrigation, no orthograde colonic lavage was performed. Bowel contents were merely milked via the elephant tube into the waste bag until colonic decompression was deemed to be sufficient.

Colorectal resection and anastomosis were performed in the standard fashion. Thirty-two patients had radical left colectomy with intraoperative irrigation; 27 had radical left colectomy without intraoperative irrigation. All patients underwent primary anastomosis without a defunctioning stoma. The site of tumour, type of resection, Dukes' staging, morbidity and mortality, as well as the functional results were compared. Postoperative mortality was defined as death occurring within 30 days of operation.

Results

There were 20 men and 12 women in the group receiving irrigation (group 2) and 12 men and 15 women in the group having no irrigation (group 1). The median age was 60 (range 24–85) years and 68 (range 24–87) years in groups 2 and 1 respectively. In group 2 there was one patient with a Dukes stage A tumour, five with stage B, 17 with stage C and nine with stage 'D', while group 1 had 0, 12, 11 and four respectively. The location and operative procedure performed are outlined in *Table 1*. *Table 2* shows the postoperative complications in the two groups.

Table 1 Location and operative procedure performed for obstructing tumours

	No irrigation ($n = 27$)	Irrigation ($n = 32$)
Location		
Splenic flexure	4	4
Descending colon	7	7
Sigmoid colon	16	21
Operation		
Left hemicolectomy	11	11
Anterior resection	16	21

Table 2 Mortality and morbidity for obstructing left-sided tumours

	No irrigation ($n = 27$)	Irrigation ($n = 32$)
No. of deaths	0	1
Morbidity		
Chest infection	1	1
Wound infection	0	1
Urinary tract infection	1	0
Anastomotic leak	0	1*
Prolonged ileus	0	0
Total	2	3

*This was in the patient who died

Median operating time was 115 (range 70–170) min for group 2 and 140 (range 75–240) min for group 1 ($P < 0{\cdot}05$, Mann–Whitney U test). Median hospital stay was 14 days in both groups with a range of 8–36 days for group 2 and 10–30 days for group 1. There were no significant differences in perioperative morbidity or mortality between the two groups, although one patient in group 2 had an anastomotic leak and subsequently died.

Discussion

Intraoperative irrigation requires almost obsessive care to avoid spillage, necessitates the use of large volumes of irrigation fluid with the possibility of electrolyte and fluid maladjustment, causes temperature control problems as well as involving a prolonged operating time. The technique is therefore not universally practised.

Several recent studies have failed to demonstrate any relationship between anastomotic dehiscence and the method or adequacy of bowel cleansing[2,4–6]. Perfect preparation of the colon may not therefore be necessary. Decompression of the main bulk of colonic contents, especially hard stools, might be sufficient to allow a safe anastomosis. There was no anastomotic leak in the group

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Paper accepted 18 September 1995

of patients having no intraoperative irrigation, despite the presence of remnant faecal matter, whereas one patient leaked in the group receiving irrigation, despite a clean colon.

This study has shown that an anastomosis can be performed safely after decompression of the obstructed colorectum alone without the need for intraoperative irrigation. The median operating time for bowel decompression without irrigation is 25 min less than that needed with irrigation. The problem of excessive fluid and electrolyte shifts may also be avoided and, in addition, the danger of intraoperative hypothermia is decreased. This procedure is especially advantageous for the patient who is unable to tolerate massive fluid and electrolyte changes and who is in need of a shorter yet safe surgical procedure.

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British Journal of Surgery 1996, 83, 788–790

Prospective audit of discharge summary errors

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During an 8-month interval of prospective audit, 63 of 637 (10 per cent) vascular discharge summaries were found to contain 94 errors. These comprised 11 (12 per cent) general errors, 21 (22 per cent) diagnostic errors, 19 (20 per cent) operative data errors, 19 (20 per cent) cases of incorrect clinical text information, 14 (15 per cent) missed complications and 10 (11 per cent) concerning follow-up arrangements. Overall, 2 per cent of consultant discharge summaries contained errors compared with 7 per cent for the senior registrar, 10 per cent for registrars and 17 per cent for senior house officers. Given that the majority of discharge summaries are currently prepared by junior staff, this study suggests that verification of the accuracy of clinical and management data should be an essential component of departmental audit meetings.

Audit has assumed an increasingly important role in medical practice. While considerable attention is directed towards identifying, reviewing and preventing inpatient morbidity and mortality, surprisingly little emphasis, despite recommendation[1], is placed on ensuring the dissemination of correct information contained in discharge summaries to family doctors. Moreover, because the coding information included on computer-generated discharge summaries often forms the basis of hospital, regional and national audit data, the requirement for accuracy is essential.

To address this issue, the accuracy of 637 discharge summaries was audited prospectively over an 8-month interval in a single surgical unit.

Materials and methods

The vascular surgical unit at Aberdeen Royal Infirmary, UK (staffed by three consultants, one senior registrar, one registrar, and one senior house officer (SHO)) provides a centralized vascular and renal transplant service to 600 000 people in north-east Scotland.

Patients discharged from the unit are given a handwritten discharge letter detailing diagnoses, treatment and medication on discharge. This is followed by a standardized computer-generated letter which is produced on a PC-based system using the Expandable Medical Audit System (EMAS). EMAS is based on the database DataEase (DataEase International, Ilford, UK) and uses the Read Clinical Thesaurus (Computer Aided Medical Systems, Loughborough, UK). This system has been used at Aberdeen Royal Infirmary since 1991. Data were entered onto a standardized form by medical staff and entered into the computer by secretarial staff. Data entered included the responsible consultant, presenting complaint, principal complaint, principal diagnoses, operative or procedural interventions, complications, changes to medication and follow-up plans. In addition, free text was added at the discretion of the medical staff to ensure adequate explanation of patient management. Between 20 January and 20 September 1994 a prospective audit was undertaken of the accuracy of 637 discharge summaries. Each week a formal unit audit meeting was held. A draft summary from each patient discharged from the vascular unit during the preceding week was critically reviewed to ensure accuracy of information and coding. Any error was identified and then corrected before sending the final discharge summary to the family doctor.

Results

Some 107 of 637 (17 per cent) summaries were produced by the three consultants: 200 (31 per cent) by one senior registrar, 118 (19 per cent) by two registrars and 212 (33 per cent) by three SHOs. After review, 63 of 637 (10 per cent) discharge summaries were found to contain 94 errors, including 11 (12 per cent) general errors, 21 (22 per cent) diagnostic errors, 19 (20 per cent) operative data errors, 19 (20 per cent) cases of incorrect clinical text information, 14 (15 per cent) missed complications and ten (11 per cent) concerning follow-up arrangements. General errors included: wrong patient name ($n = 1$); wrong responsible consultant ($n = 7$); failure to copy to other medical staff involved in patient care ($n = 2$) and describing the wrong symptomatic leg ($n = 1$). Diagnostic errors arose in three ways (*Table 1*): incorrect diagnosis ($n = 9$); missed diagnosis ($n = 9$) and coding errors ($n = 3$). Similarly, operative data errors (*Table 2*) involved the wrong operations ($n = 5$); missing operations ($n = 8$); wrong coding ($n = 4$) and failure to detail important

Table 1 Diagnostic errors on discharge summaries

Incorrect diagnoses ($n = 9$)	
Incorrect	*Correct*
Rest pain	Gangrene
Rest pain	Venous ulcer
Rest pain	Claudication
Rest pain	Claudication
Arm pain	Infected dialysis fistula
Varicose veins	Venous ulcer
Dysphagia	Dysphasia
Groin swelling	Infected haematoma
Claudication	Rest pain
Coding errors ($n = 3$)	
Incorrect	*Correct*
Urethral rupture	Ureter (transplant) rupture
Benign mesonephroma	Polycythaemia
Arteriosclerotic disease	Occluded axillofemoral graft
Missed diagnoses ($n = 9$)	
Abdominal aortic aneurysm	Chronic venous insufficiency
Diverticular mass	Varicose veins
Anastomotic femoral aneurysm	Severe angina
Transient ischaemic attacks	Rest pain ($n = 2$)

Presented to the Royal College of Surgeons of Edinburgh, in Edinburgh, UK, March 1995 and the Association of Surgeons of Great Britain and Ireland, in London, UK, May 1995
Paper accepted 31 August 1995

Table 2 Operative errors on discharge summaries

Wrong operation ($n = 5$)	
Incorrect	*Correct*
Iliac bypass ($n = 2$)	Iliodistal bypass
Angioplasty	Angiogram
Graft excision	Revision dialysis fistula
Axillofemoral bypass	Axillobifemoral bypass
Coding errors ($n = 4$)	
Incorrect	*Correct*
Reimplantation of native kidney	Reimplantation of ureter
Non-specific iliac operation	Angioplasty
Repair acquired arteriovenous fistula	Forefoot amputation
Femoral artery bypass	Aortofemoral bypass
Missed operations ($n = 8$)	
Fasciotomy ($n = 2$)	
Closure of fasciotomy	
High saphenous ligation and avulsions	
Femoral thrombectomy ($n = 3$)	
Feeding gastrostomy	
Important intraoperative findings not listed ($n = 2$)	
Rectal bleeding: no intra-abdominal pathology noted	
Diverticular mass: no mention of consultant general surgical advice	

intraoperative findings concerning coexistent pathology ($n = 2$). Important complications were omitted in 14 patients. These included six general complications: postoperative angina; pyrexia of unknown origin; *Streptococcus faecalis* septicaemia; transfusion reaction; grand mal seizure and a vasovagal attack sufficient to cause abandonment of an angiogram. Similarly, eight vascular complications causing prolonged inpatient stay were not detailed, including groin wound haemorrhage and haematoma ($n = 2$), groin seroma ($n = 1$), leg wound dehiscence and necrosis ($n = 2$), acute postoperative limb ischaemia ($n = 1$), severe hypertension after carotid endarterectomy ($n = 1$) and 'trashing' as a result of microembolism ($n = 1$). Follow-up information was erroneous in ten patients. Three were given the wrong clinic date, one would have attended the wrong clinic, one was given an unnecessary review appointment, three were inadvertently discharged from review while, in two, arrangements had been made to fly patients to Aberdeen from Orkney and Shetland when follow-up was possible on their own islands.

Seventeen patients had important errors in the free text. These fell principally into two categories: incomplete explanation of patient care ($n = 10$) and wrong information ($n = 9$). Incomplete data included: failure to disclose important investigation results ($n = 2$), poor explanation of management decision ($n = 7$) and failure to disclose that a patient had refused amputation ($n = 1$). Examples of wrong information included: listing the wrong level of arterial disease ($n = 3$), e.g. aortoiliac instead of distal tibial; incorrect medication advice ($n = 4$), usually concerning anticoagulation; and two patients were put on the waiting list for the wrong operation. Overall, two of 107 (2 per cent) consultant summaries contained errors compared with 13 of 200 (7 per cent) prepared by the senior registrar, 12 of 118 (10 per cent) by the registrars and 36 of 212 (17 per cent) by SHOs. The more junior the person performing the discharge the more likely they were to make errors (χ^2 test for trend: $P < 0{\cdot}01$). However, it was not possible to demonstrate that error rates increased following staff rotations.

Discussion

The advent of user-friendly, affordable personal computers has allowed the easy analysis of large amounts of data and has the added advantage of allowing the generation of standardized discharge summaries[2,3]. These pro-forma discharge letters are comprehensive and well received by general practitioners (GPs)[4,5].

In addition to the detrimental effect on the quality of local and national audit data, many errors are clinically important with implications for patient care. Furthermore, they have financial and medicolegal implications. The GP's impression of a unit is dependent, in part, on the quality of the discharge summaries. Poor quality summaries with mistakes (obvious or disguised) reflect poorly on the unit from which they originate. In this unit the vast majority of discharge summaries are prepared by junior staff (83 per cent by three juniors *versus* 17 per cent by three consultants). Over 90 per cent of the summaries were adequate. This compares favourably with those reviewed from a medical unit[6]. Errors, however, do occur and cover a wide range.

Failure to identify correctly the responsible consultant unnecessarily complicated follow-up arrangements. Failure to document indicators of critical limb ischaemia such as rest pain, ulceration and gangrene may result in delay in the management of these patients with a resultant increased morbidity. Incorrect clinic appointments lead to inconvenience and confusion for patients. Poor prescription advice, particularly when concerning anticoagulants, is potentially dangerous.

The reasons for the errors are multiple. With decreasing hours, cross-cover and holidays, junior doctors often perform summaries on patients with whom they are not familiar. Disordered casenotes with multiple entries can make it difficult to identify relevant facts. Dictated and typed operating notes may not have found their way to casenotes by the time of summary preparation. These errors could have been avoided if the standardized form, on which the summary is based, had been completed during admission and not left until the time of summary preparation. In addition, many juniors cannot relate to the importance of an accurate computerized database and, when faced with a pile of discharges, may be unwilling to make the effort to identify the specific code. Codes are not easily interpreted and handwritten codes can easily be misread. In this series, for example, a simple coding error led to polycythaemia being mistakenly identified as a benign mesonephroma.

The Read code system used to generate the letters also forms the basis for local audit. It codes to five digits thereby, in theory, allowing greater specificity of coding than the four-digit systems (International Classification of Diseases, Injuries and Causes of Death (ICD) Version 9 (HMSO, London, UK) and Office of Population Censuses and Surveys (OPCS) Version 4 (HMSO, London, UK)) currently used in this hospital to compile national data. In addition, the Read code system permits coding of diagnoses, procedures and complications in comparison with separate systems for diagnoses (ICD-9) and procedures (OPCS4). The structure of the database and the 'doctor-friendly' nature of the coding system mean that searching the system for a suitable code is relatively easy. It has a disadvantage in being computer-based with no book reference form. This is partially overcome by having lists of commonly used codes, but finding unfamiliar codes requires access to, and knowledge of, the coding database.

Errors of patient details and the responsible consultant could potentially be avoided if these could be downloaded from the hospital's main patient administration computer system. This is possible either by linking the systems or simply copying and transferring the details using a floppy disk. The authors' unit, unlike others in the hospital, is not currently linked and disk transfer, although technically possible, is not available as a routine service.

That the potential for error is inversely related to clinician grade is important when it is considered that the majority of discharge summaries in this unit (and probably in most others in this country) are prepared by junior staff. This emphasizes the importance of some method of verifying the content of the summaries. Until the introduction of this process, summaries were only checked by the person who dictated them.

In addition to verifying discharge summaries the authors' weekly meeting has other advantages. Reviewing letters forms the basis for discussion of patient management, allowing inter-consultant exchange and junior education. It also ensures that discharges (in addition to the handwritten note given to the patient) are dispatched within 2 weeks of patient discharge.

Patient discharge summaries should be prepared by someone familiar with the patient. Complex summaries should be done by the responsible consultant. Furthermore, surgical trainees should be educated in the use of, and benefits from, an accurate local database. The standardized form should be completed as the admission progresses (particularly important with regard to procedures and complications). A method of quality control is essential and easily accomplished by the method outlined.

Acknowledgements

E.M.C. is a University of Aberdeen ACT research fellow.

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British Journal of Surgery 1996, 83, 791–795

Blood flow in the lower limb after balloon angioplasty of the superficial femoral artery

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Using duplex ultrasonography lower-limb blood flow measurements were obtained in 20 patients with intermittent claudication. Assessments of flow were made in the common femoral artery, profunda femoris artery (PFA) and superficial femoral artery (SFA) before and after angioplasty for stenoses of short segments of the SFA. Blood flow was measured at rest and after exercise on a cycle ergometer. Collateral flow was calculated using an established mathematical model. Results were compared with the ankle:brachial systolic pressure index (ABPI) after exercise. Although there was no overall increase in resting limb blood flow, an increase in mean(s.d.) SFA flow from 148(79) to 312(94) ml min^{-1}, with a concomitant decrease in PFA flow from 224(84) to 98(43) ml min^{-1} was noted 1 week after angioplasty ($P < 0{\cdot}05$). At rest there was an increase in mean(s.d.) ABPI from 0·62(0·12) to 0·89(0·23) ($P < 0{\cdot}05$). Collateral flow was estimated to have decreased from 186(34) to 18(8) ml min^{-1}; the pattern of change in flow was similar after exercise. Angioplasty of the SFA remains controversial because of the risk of restenosis. The above methodology allows assessment of whether patients can re-establish collateral flow or whether limb blood flow will be significantly compromised if restenosis occurs.

Percutaneous transluminal angioplasty (PTA) is now the treatment of choice for stenosis and localized arterial occlusion in the iliac system. For disease in the superficial femoral artery (SFA), despite immediate relief of symptoms, the technique remains controversial because of the relatively high restenosis rate[1,2]. Both angioscopy[3] and intravascular ultrasonography[4] have demonstrated vessel damage after PTA.

There are few data on the haemodynamic changes that occur after PTA. In most centres, the only test made routinely is measurement of the ankle:brachial systolic pressure index (ABPI)[5]. This index gives an objective and quantitative assessment of the success of angioplasty by indicating improvement of flow into the calf and foot via the SFA. However, the ABPI does not provide haemodynamic information on alteration of flow in the previously stenosed SFA, or give an indication of whether the procedure has increased total blood flow to the limb.

There is general agreement that in the presence of severe stenosis or occlusion of the SFA, the profunda femoris artery (PFA) can, through the development of a collateral circulation, supply the lower leg and foot. This is reflected by enlargement of the PFA, which may be seen in angiograms, in patients with SFA occlusion[6]. Recent advances in duplex ultrasonography have allowed blood flow to be measured not only in the common femoral artery (CFA) but also in both the SFA and PFA[7]. The aim of this study was to evaluate the effect of superficial femoral angioplasty on blood flow in these three arteries and to quantify the changes in the collateral circulation.

Patients and methods

Patients

Blood flow measurements were made in 22 patients who underwent balloon angioplasty for stenoses of short segments of the SFA with a mean(s.d.) length of 4·5(0·8) cm. Median age of the patients was 66 (range 52–79) years; there were 16 men and six women. All had had disabling intermittent claudication for at least 6 months, although none had rest pain. Angiography demonstrated no evidence of significant aortoiliac disease and a normal PFA. Patients were studied just before PTA and at 1 week and 1, 3 and 6 months after the procedure. All angioplasty procedures were performed by the crossover technique to prevent a haematoma from affecting flow measurements. Two late studies were not performed for the following reasons: one patient sustained a myocardial infarction after 2 months and a second developed bladder cancer requiring chemotherapy.

Protocol

Local ethical committee approval was obtained and patients gave informed consent before each study. For the purposes of the study, patients were asked to refrain from stimulants such as tea and coffee for 4 h before flow measurements. After 20 min of supine rest, the femoral vessels were scanned and flow calculated in the CFA, SFA and PFA. To monitor cardiac activity, blood pressure and pulse were recorded non-invasively throughout the study using an automated system. After resting flow measurements were obtained, the patients underwent a 5-min period of exercise on a cycle ergometer. This consisted of cycling between 40 and 70 revolutions per minute (r.p.m.) with a 1–1·5-kg load for 5 min. Cycling is known to increase PFA flow preferentially[7]. Thigh exercise was used as it allows an increase in the total work by the leg to a greater extent than standard treadmill testing, as the patient is not affected by ischaemic pain in the calf early during the exercise. Under these circumstances flow remains at a higher level for a longer period on cessation of exercise giving a greater opportunity to assess changes in flow.

Each patient underwent the same quantity of work at each visit. Immediately after exercise the patient adopted the supine position so that volumetric flow measurements from all three major arteries could be reassessed. The ABPI at rest and after exercise was also measured using a standard technique[8].

Blood flow measurements

Flow measurements were taken by one observer using an ATL (Advanced Technological Laboratories, Seattle, Washington, USA) Ultramark 9 High Definition Imaging colour duplex

Paper accepted 4 September 1995

Doppler ultrasonographic scanner equipped with a linear array 5-MHz probe. Flow was taken to be the product of 'time-averaged mean velocity' and arterial cross-sectional area[9]. Mean velocity was obtained by opening the Doppler gate such that it encompassed the entire vessel. This was averaged over five cardiac cycles to give the time-averaged mean velocity. Cross-sectional area was estimated by measuring the vessel diameter from one intimal surface to the other by means of on-screen callipers. The vessel was imaged in longitudinal section and the screen image frozen in systole to obtain diameter measurements. When making measurements care was taken to avoid areas of atherosclerosis so that the vessel could be assumed to be circular in cross-section.

A separate study was performed in 20 normal volunteers by two observers, one of whom performed the flow measurements in the patient group, to assess the observer variability of flow measurements. Measurements were taken of flow in the CFA, SFA and PFA by each observer on two separate occasions. The intraobserver coefficients of variation of volumetric flow were 15, 14 and 23 per cent for the CFA, SFA and PFA respectively.

Collateral flow

Collateral flow was estimated using a four-element lumped parameter mathematical model (*Fig. 1*). This model was used to estimate collateral flow before and after angioplasty[10]. As none of the patients had evidence of atherosclerosis of the PFA, resistance of this vessel was taken to be zero. Common femoral arterial pressure was assumed to be equivalent to mean systemic pressure, which it is in the supine position. In this position mean venous pressure (which is caused by hydrostatic pressure) can also be taken to be zero. Given flow into the two arms of the model before and after angioplasty of the SFA and mean blood pressure, resistance of the thigh, calf and collateral circuits was calculated as a function of SFA resistance. These can be assumed not to change after angioplasty of the SFA. SFA resistance, the variable resistance, reduces considerably after successful angioplasty of the SFA as the bulk of the resistance is located at the site of the stenosis.

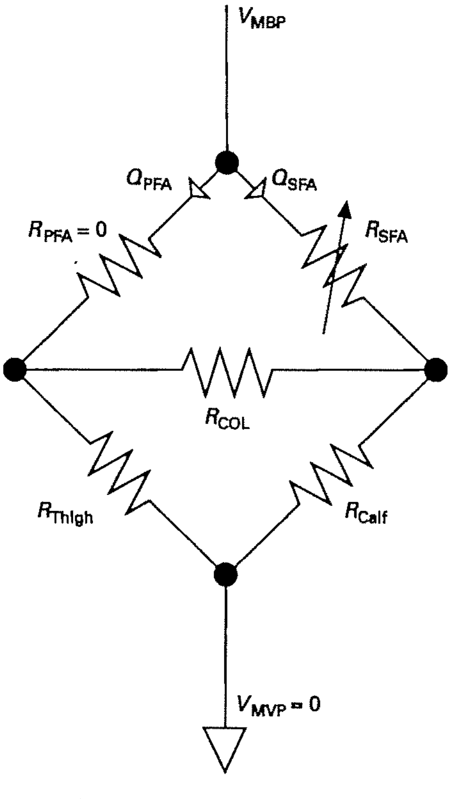

Fig. 1 Mathematical model used to calculate collateral flow. *Q*, flow; *R*, resistance; *V*, pressure; MVP, mean venous pressure; MBP, mean blood pressure; COL, collateral pathway; PFA, profunda femoris artery; SFA, superficial femoral artery; $\nearrow\!\!\!\!\sim$, variable resistance

The model was established as a set of equations in Mathcad (Mathcad, Bristol, UK) 4.0 (a mathematical software package). Given the values for mean blood pressure and flow the equations were solved. It was found that solutions existed and changed very little for reductions in SFA resistance greater than 40-fold. Therefore, SFA resistance was assumed to decrease at least 40-fold after angioplasty of this vessel. By the use of the mathematical model collateral flow (Q_{Col}) can be calculated from the equation:

$$Q_{\mathrm{Col}} = \frac{V_{\mathrm{MBP}}}{R_{\mathrm{Col}}}\left(\frac{R_{\mathrm{T}}}{R_{\mathrm{PFA}}+R_{\mathrm{T}}} - \frac{R_{\mathrm{CALF}}}{R_{\mathrm{CALF}}+R_{\mathrm{SFA}}}\right)$$

where V_{MBP} = mean blood pressure, R_{Col} = collateral resistance, R_{T} = thigh resistance, R_{PFA} = PFA resistance, R_{CALF} = calf resistance, R_{SFA} = SFA resistance.

To estimate collateral flow after exercise the following modifications were made to the model based on the changes in total limb peripheral resistance (calculated from CFA flow). First, the ankle pressure was assumed to be equal to popliteal pressure as there was no evidence of disease in the calf vessels in the patients. Second, the resistance of the calf and thigh decreased by at least a factor of 0·25 after exercise (based on the decrease in total peripheral resistance).

Statistical analysis

Results of flow determinations are expressed as mean(s.d.) ml min^{-1}. Comparison between groups was undertaken using the paired *t* test. Bonferroni's correction was used for multiple analysis with preangioplasty values. Linear regression was used to assess the relationship between the increase in ABPI measurement and blood flow. $P < 0{\cdot}05$ was considered to be statistically significant.

Results

All patients had a technically successful angioplasty without complications. There was an immediate improvement in symptoms in all cases. A significant increase in exercise ABPI from the mean(s.d.) preangioplasty level of 0·62(0·12) to 0·89(0·23) 1 week after angioplasty ($P < 0{\cdot}05$) (*Fig. 2*) was observed. Although ABPI after exercise increased further at 1 month to 0·98(0·32), this was not statistically significant compared with that at 1 week. There was no further significant increase in the values recorded at 3 and 6 months.

The angioplasty procedure produced no increase in overall resting limb blood flow, as indicated by flow in the CFA (*Fig. 3*). There was a significant increase in mean(s.d.) resting SFA flow from 148(79) to 312(94) ml min^{-1} ($P < 0{\cdot}05$). In contrast, there was a marked and persistent decrease in mean(s.d.) PFA flow after angioplasty from 224(84) to 98(43) ml min^{-1} ($P < 0{\cdot}05$, paired *t* test).

Flow in the CFA after exercise was also not significantly increased from preangioplasty levels (*Fig. 4*). Mean(s.d.) flow after exercise in the SFA rose from 552(196) to 963(284) ml min^{-1} ($P < 0{\cdot}05$). Flow in the PFA decreased from 771(247) to 308(98) ml min^{-1} ($P < 0{\cdot}005$, paired *t* test). As with resting flows, flows after exercise showed no further change throughout follow-up.

There was a close correlation between the percentage increase in ABPI when plotted against the percentage increase in SFA flow before and after angioplasty ($r = 0{\cdot}86$, $P < 0{\cdot}05$) (*Fig. 5*).

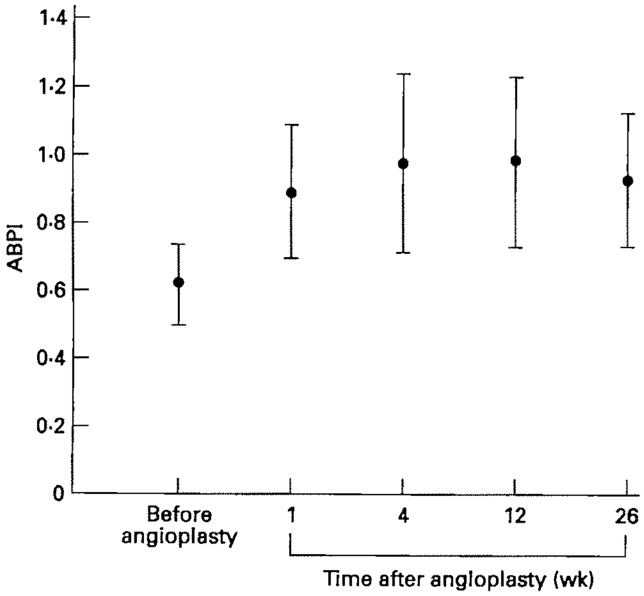

Fig. 2 Mean exercise ankle : brachial pressure indices (ABPI) before, and at 1, 4, 12 and 26 weeks after angioplasty. Error bars represent s.d.

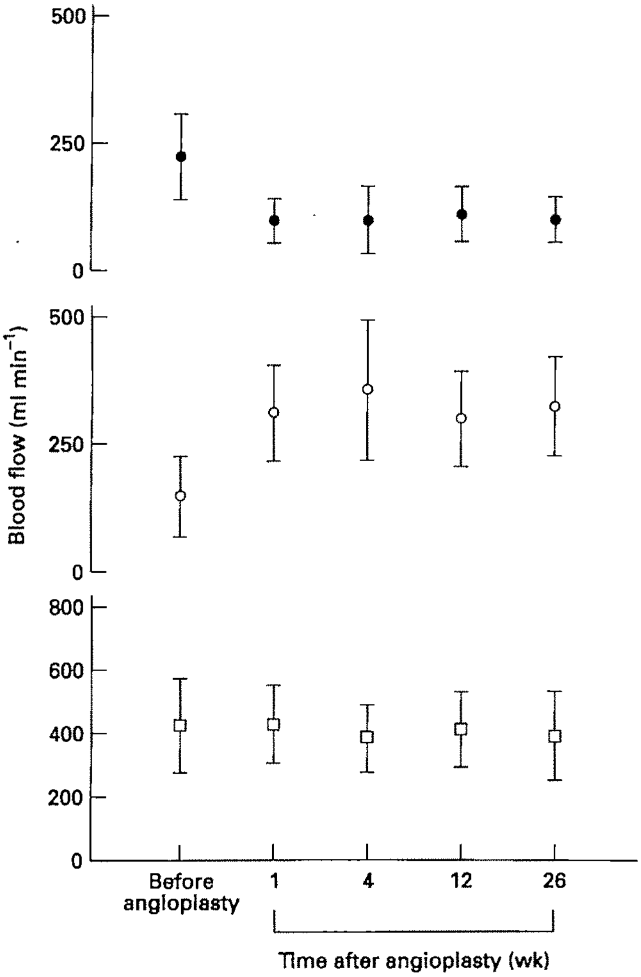

Fig. 3 Mean resting blood flow measurements in the common femoral artery (□), superficial femoral artery (○) and profunda femoris artery (●) before and at 1, 4, 12 and 26 weeks after angioplasty. Error bars represent s.d.

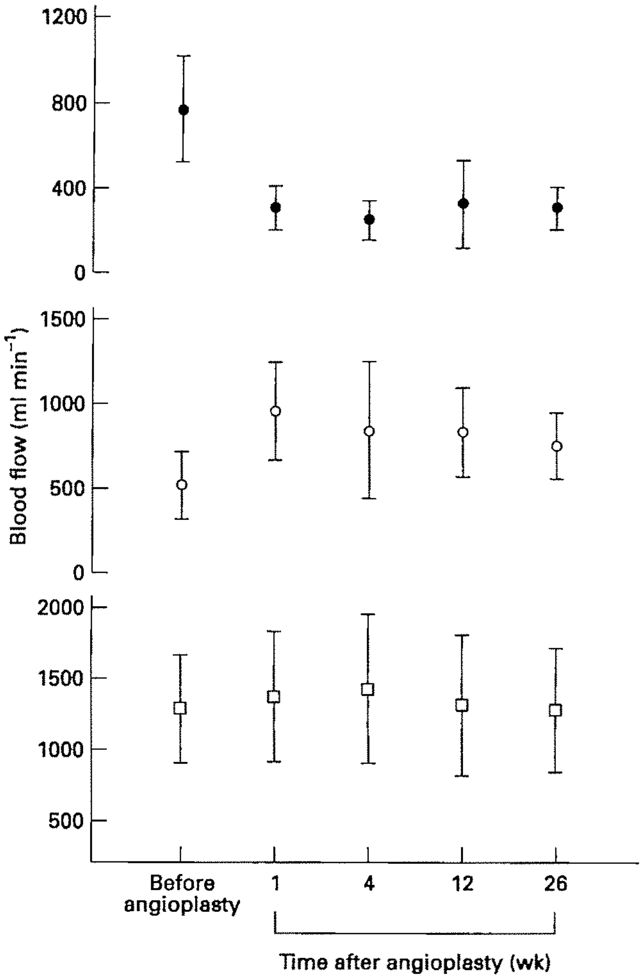

Fig. 4 Blood flow measurements after exercise in the common femoral artery (□), superficial femoral artery (○) and profunda femoris artery (●) before and at 1, 4, 12 and 26 weeks after angioplasty. Error bars represent s.d.

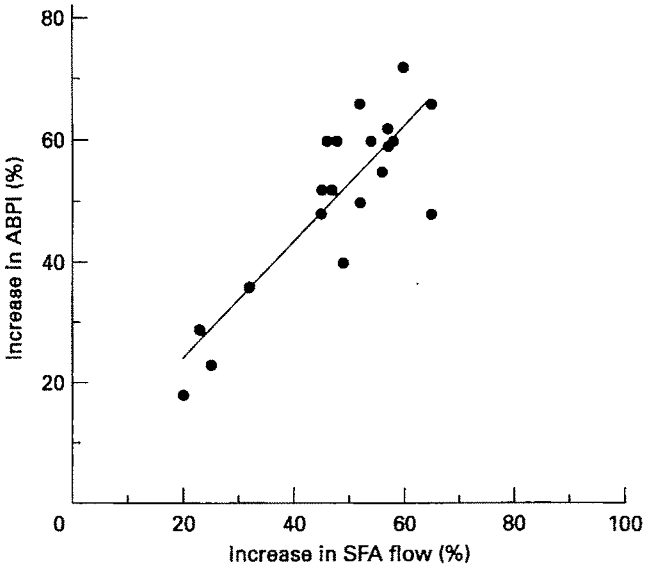

Fig. 5 Relationship between the increase in blood flow in the superficial femoral artery (SFA) and exercise ankle : brachial systolic pressure index (ABPI) 1 week after angioplasty ($r = 0{\cdot}86$, $P < 0{\cdot}05$, linear regression)

By means of the mathematical model, mean(s.d.) resting collateral resistance was calculated to be 0·16(0·03) mmHg ml^{-1} min with a calf resistance of 0·25(0·12) mmHg ml^{-1} min and a thigh resistance of 0·92(0·32) mmHg ml^{-1} min. Mean(s.d.) SFA resistance before angioplasty was estimated to be 0·069(0·025) mmHg ml^{-1} min. Resting collateral blood flow was estimated to have decreased from 186(34) to 18(8) ml min^{-1} at 1 week after angioplasty with a further reduction to 11(9) ml min^{-1} at 1 month ($P < 0{\cdot}005$). Mean(s.d.) collateral flow after exercise was estimated to be 258(49) ml min^{-1} before angioplasty and to have declined to zero after angioplasty.

Discussion

Although volumetric flow measurements using duplex ultrasonography have been available for some years[11], it is only recently, with improved on-screen resolution and advanced integral software, that reliable instantaneous flow measurements have been possible. As ultrasonography is non-invasive and painless it can be repeated easily, allowing flow under normal physiological settings to be studied.

Total limb blood flow has previously been measured before and after angioplasty using a radiolabelled isotope technique. A study of 101 limbs undergoing angioplasty, which included angioplasty of the SFA, reported an overall lack of improvement in total limb blood flow[12]. Although this technique is invasive, it is highly reproducible. However, flow was measured after a period of occlusion hyperaemia and so not studied under normal physiological conditions.

For the purpose of the present study, observer variability was assessed separately on 20 normal volunteers, who were each scanned twice by two observers. Normal participants were deemed suitable for this purpose because all blood flow measurements have to be made away from areas of atherosclerosis. Such areas of disease distort the cross-section of the vessel, making the assumption that the cross-sectional area is circular in the calculation of blood flow untenable[9]. The intraobserver coefficients of variation of volumetric flow were 15, 14 and 23 per cent for the CFA, SFA and PFA respectively. Although these reproducibility values seem high, the consistency and magnitude of the blood flow changes after angioplasty demonstrate that important changes in regional flow had occurred.

This study has shown that total limb blood flow after angioplasty of the SFA remains unchanged at rest and after exercise. In addition, the improvement in symptoms after angioplasty is associated with an increase in flow in the SFA not only at rest but also after exercise. If total limb blood flow does not change, the increase in flow must inevitably be associated with a similar decrease elsewhere, with symptoms resolving because blood is diverted through a pathway of lesser resistance. A corresponding decrease in blood flow in the PFA was found in this study.

In patients with SFA occlusion the PFA is the major source of supply to the collateral pathway, and can provide sufficient blood to meet tissue requirements at rest and, in some asymptomatic patients, even the increased demands during exercise[13]. Because of the nature of the collateral system, the flow through it is difficult to quantify. In 1970 Sumner and Strandness[14] estimated collateral resistance in patients with isolated SFA occlusion. Their mathematical model was similar to the one used in this study. Although they were able to study the effect of the collateral resistance on limb blood flow, they were unable to measure PFA flow and thus estimate collateral flow. The data from the present study have enabled collateral flow to be quantified not only at rest but also after exercise, and confirmed that collateral flow is virtually abolished at rest after angioplasty of the SFA and is zero after exercise. The further decrease in flow after exercise is likely to be due to the diversion of blood to the dilated vascular bed of exercising muscle[15].

The ankle arterial systolic pressure after exercise is related to the severity of disease[16] and is still useful in indicating the improvement in flow after surgery or angioplasty. The data in the present study illustrate that improvement in symptoms is accompanied by an increase in the ABPI value after exercise. Maximum improvement in the ABPI occurs up to 1 month after angioplasty[17], and this finding was corroborated in the present study. A close correlation between the improvement in ABPI and SFA blood flow after angioplasty was observed, confirming that ABPI measurements are a reasonable indicator of blood flow in the SFA (*Fig. 5*).

Assessing collateral flow using the model outlined in this study provides a means of non-invasively assessing the consequences of lower-limb revascularization. It may allow a more informed decision about treatment.

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Announcement

The Rouleaux Club

The Rouleaux Club is a society for surgical trainees who have an interest in vascular surgery. The club meets twice a year, once for a weekend meeting in summer and once at the Vascular Surgical Society in November.

The club provides a social setting where members meet and find mutual support especially in areas related to vascular research. The club is increasingly seen as the mouthpiece of vascular trainees and as such we wish to ensure that all trainees with a vascular interest have the opportunity to join.

All surgical registrars, research fellows or senior registrars with an interest in vascular surgery are invited to join the Rouleaux Club. Membership is free.

Please address all enquiries to: Mr Mark Whiteley, Secretary, The Rouleaux Club, Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK.

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Case report

Iliac arteriovenous fistula following lumbar disc surgery treated by percutaneous endoluminal stent grafting

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Trauma to the aorta, inferior vena cava and iliac vessels is a recognized complication of lumbar disc surgery due to penetration of the anterior longitudinal ligament during curettage. The first case is reported of an arteriovenous fistula following discectomy treated by percutaneous transluminal stent grafting.

Case report

A 64-year-old man presented 4 years after lumbar discectomy of the L4–5 disc with cardiac failure and left-sided intermittent claudication. Diagnostic arteriography demonstrated a large fistula between the left common iliac artery and vein (*Fig. 1a*). Under local anaesthesia, a 12-mm diameter 6-cm long nitinol stent graft (Cragg EndoPro; MinTec, Bahamas) was introduced via a 10-Fr percutaneous introducer sheath in the left common femoral artery. By means of the technical method described by Henry *et al.*[1], the self-expanding stent graft was successfully deployed in the left common iliac artery, covering the mouth of the fistula. Balloon dilatation within the stent was required to oppose the graft material fully against the arterial wall. Check arteriography 1 month later confirmed that the fistula remained closed (*Fig. 1b*). Chest radiography similarly showed complete resolution of the cardiac failure.

Paper accepted 5 October 1995

Discussion

Major vascular trauma complicating lumbar disc surgery was first described[2] in 1945. It has also been reported following cervical disc surgery[3]. In the aortoiliac segments, immediate sequelae include postoperative hypotension and death from exsanguination. Late consequences include false aneurysm and arteriovenous fistula. Fistulas commonly present with cardiac failure or rarely, as in the present patient, with intermittent claudication. This rare complication may be preventable by preoperative computed tomographic measurement of the disc at the time of diagnostic scanning[4].

In their review of 70 published cases of vascular complications of disc surgery, Raptis *et al.*[5] found that only 24 patients presented with acute haemorrhage. The remaining two-thirds presented late with arteriovenous fistula. Established treatment is surgical exploration, repair of the arterial defect and/or arterial grafting.

With the development of commercially available stent grafts, iliac false aneurysm and arteriovenous fistula can now be effectively treated by a percutaneous endovascular procedure as the treatment of choice. It is likely that, in the near future, technology will enable similar stent grafting of aortocaval fistula.

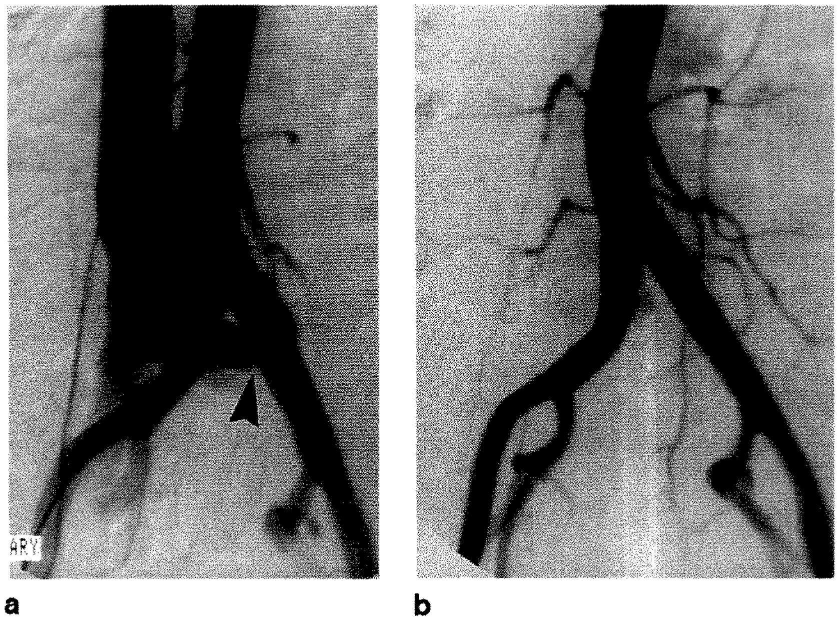

Fig. 1 Digital subtraction arteriograms showing **a** the left common iliac arteriovenous fistula (arrowhead) before treatment and **b** occlusion of the fistula following stent grafting

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British Journal of Surgery 1996, **83**, 797

Surgical workshop

Skin from the amputated limb should not be wasted

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Patients who need limb amputation for ischaemia often have bilateral disease with contralateral ulceration which might benefit from skin grafting. A report is made of four cases where this was accomplished with the use of skin grafts taken from the amputated limb.

Surgical technique

At the time of limb amputation, a split-thickness skin graft was taken with a Humby knife from viable skin on the limb to be amputated. The ulcerated area on the remaining limb was debrided down to bleeding tissue and the graft positioned either at the time of amputation or a day or two later on the ward using standard skin grafting techniques. Excess skin graft material was then stored in a saline-soaked swab in a refrigerator at 4°C for later use.

The procedure was used in four patients: three had leg amputation for critical ischaemia, and one was diabetic and had severe necrosis and cellulitis following infection of a heel pressure sore. There were three below-knee and one above-knee amputations. In all patients there was an initial skin graft take of at least 50 per cent (*Fig. 1*), although one required regrafting with skin stored from the previous harvest.

Discussion

Most leg amputations are for critical ischaemia with gangrene. Other indications include diabetic skin ulcers and penetrating decubitus ulcers. Patients requiring amputation often have contralateral chronic skin ulcers which impair rehabilitation and require regular dressing with resultant increased stay in hospital or district nurse attention. Skin grafting accelerates healing and provides protection against infection. The use of viable skin from a limb to be amputated is an option which should be considered as there is often a good supply of skin and, obviously, no morbidity from donor site problems. Vascular surgeons should be reminded of the opportunity of gaining positive benefit from an operation often thought of as a disaster.

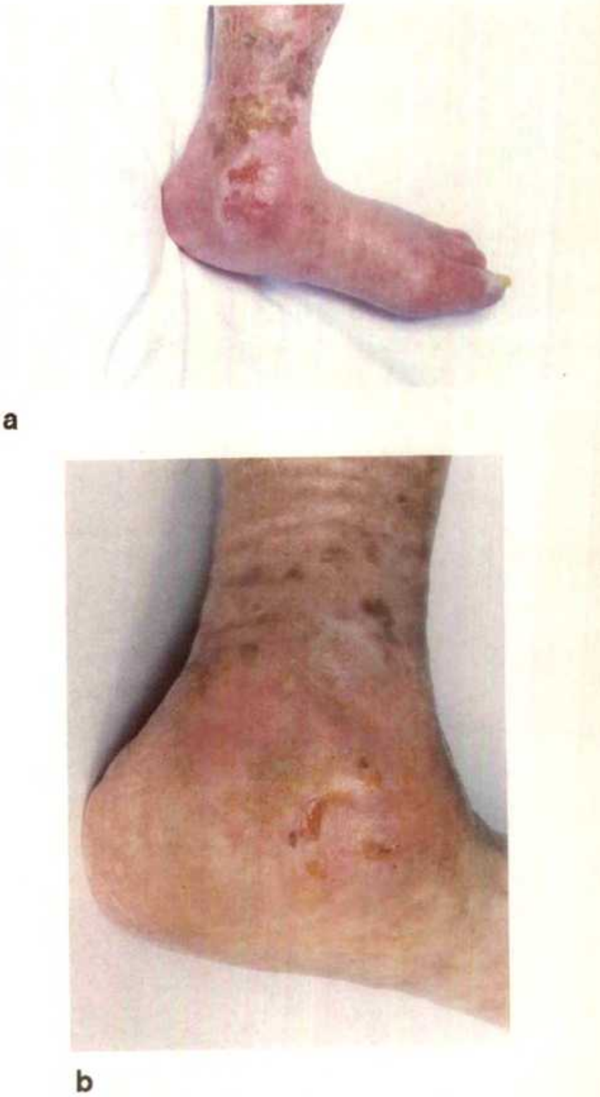

Fig. 1 **a** Fifty per cent take of skin graft on medial malleolar ulcer 4 weeks after contralateral above-knee amputation. **b** After a second graft using stored skin, healing was almost complete

Paper accepted 5 October 1995

British Journal of Surgery 1996, **83**, 798–802

Xanthine oxidase in critically ischaemic and claudicant limbs: profile of activity during early reperfusion

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Xanthine oxidase activity in blood from the ipsilateral femoral vein, and the relationship between xanthine oxidase production and the products of lipid peroxidation, were studied before operation and for 60 min following release of clamps after successful revascularization in two groups of patients with claudication or critical ischaemia. Before revascularization, detectable levels of xanthine oxidase were found only in patients with critical ischaemia. Clamping during bypass surgery led to release of xanthine oxidase in claudicants, but this activity reduced after 60 min. There was no evidence of lipid peroxidation during this time. Xanthine oxidase activity in brachial vein blood was higher than in femoral vein blood in patients with critical ischaemia before revascularization.

Successful revascularization of an ischaemic limb renders the patient susceptible to reperfusion injury syndrome. In this syndrome biochemical changes occur in the muscle which, in severe cases, may lead to rhabdomyolysis, with the release of myoglobin and other cellular proteins, and the possibility of renal complications. It is widely believed that reperfusion injury syndrome is a biphasic phenomenon[1], initiated during ischaemia and exacerbated during reperfusion. The mechanism of its development is still unclear; lipid peroxidation resulting from the action of free radicals is almost certainly involved[2], but there are other factors such as neutrophils[3], leukotriene B_4[1] and thromboxane A_2[4].

Oxygen-derived free radical-mediated tissue peroxidation has been shown to occur upon reoxygenation of an ischaemic limb[5] and xanthine oxidase has been proposed as a major source of superoxide radicals[4]. This enzyme originates from the capillary endothelium and is induced under conditions of ischaemia[6], probably by proteolytic cleavage of xanthine dehydrogenase[4]. By reducing molecular oxygen to a free radical form, xanthine oxidase catalyses the hydrolysis of hypoxanthine to xanthine and of xanthine to uric acid. This process generates the superoxide radical which may be responsible for the initiation of a peroxidation sequence[2] and ultimately the destruction of unsaturated fatty acid side-chains, resulting in the disruption of cell membranes. Peroxidation of unsaturated membrane fatty acid side-chains results in the formation of conjugated diene structures early in the peroxidation sequence. Free malondialdehyde is formed at a later stage in lipid peroxidation. These two products make useful markers of lipid peroxidation.

The aim of this study was to investigate both the role of xanthine oxidase during ischaemia and in the early phase of successful revascularization, and the relationship between xanthine oxidase production and lipid peroxidation at this early stage. This study contributes to an understanding of the different phases of reperfusion injury syndrome.

Patients and methods

The study protocol was agreed by the combined University College London Hospitals ethics committee. Informed consent to the study was obtained from all patients.

Critical ischaemia (group 1)

There were nine patients (five men, four women) of median age 71 (range 45–81) years, assessed as having critical ischaemia because of rest pain, ischaemic ulceration or digital gangrene with a median preoperative ankle:brachial pressure index (ABPI) of 0·25 (range 0·0–0·6). All patients underwent femorodistal bypass, two to the tibioperoneal trunk and the remainder to a crural artery in the lower half of the leg. Length of time of clamp application was noted.

Intermittent claudication (group 2)

Ten patients (five men, five women) of median age 71 (range 61–84) years had intermittent claudication, no rest pain and median preoperative ABPI of 0·55 (range 0·3–0·9). All patients had a femoropopliteal bypass, seven to the suprageniculate popliteal and the remainder to the infrageniculate popliteal artery. Clamp times were noted as above.

Controls (group 3)

Seven patients (four men, three women) of median age 47 (range 33–78) years undergoing varicose vein surgery were used as controls to determine normal levels of circulating xanthine oxidase, conjugated dienes and malondialdehyde.

Sampling

Femoral vein blood samples, taken by separate needle stabs and collected into heparinized tubes, were taken during reconstructive surgery before clamping, then at 2, 20 and 60 min after release of the clamps and restoration of blood flow. Brachial vein samples by separate needle stabs were also taken before clamping and 20 min after release of clamps in six patients in group 1 for comparison. One aliquot of each plasma sample, for xanthine oxidase analysis, was stored with a preservative (dithiothreitol 10 mmol l^{-1} and phenylmethylsulphonyl fluoride 1 mmol l^{-1} in phosphate buffer) in a ratio of 10 μl preservative to 1 ml plasma to prevent the *in vitro* conversion of xanthine dehydrogenase to xanthine oxidase[7].

Chemical analysis

Xanthine oxidase, conjugated dienes and malondialdehyde were assayed for each plasma sample (where there was sufficient sample). Plasma potassium (K^+) and creatine kinase levels were assayed on the same samples as conventional markers of muscle

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cell damage; creatinine concentration was measured as a marker of renal function.

Xanthine oxidase. Xanthine oxidase activity was assayed by a method adapted from that of Price *et al.*[8]. Uric acid formation was measured spectrophotometrically at a wavelength of 283 nm, at 37°C, using a hypoxanthine substrate at a final concentration of 0·1 mmol l^{-1}. The assay medium was phosphate buffer 0·2 mol l^{-1} with ethylene diamine tetra-acetic acid 0·1 mmol l^{-1} at pH 8·0. The activity of xanthine oxidase was calculated as nanomoles of uric acid produced per minute per millilitre.

Conjugated dienes. The concentration of conjugated dienes was measured spectrophotometrically[9] at a wavelength of 233 nm after extraction from 0·5 ml plasma into 7 ml 2:1 chloroform:methanol mixture. The extract (5 ml) was treated with 2 ml acidified water (pH 2·5), then 2 ml of the final chloroform extract was evaporated to dryness with a GyroVap (V. A. Howe, Breckon, UK) centrifugal evaporator. The residue was reconstituted with 0·5 ml heptane and absorbance was read against a heptane blank.

Malondialdehyde. Malondialdehyde concentrations were measured spectrophotometrically as thiobarbituric acid-reactive products[9] using 3 ml 1:1:1 solution of 15 per cent trichloroacetic acid, 0·375 per cent thiobarbituric acid and hydrochloric acid 0·25 mol l^{-1}, and 1 ml plasma. Butylated hydroxtoluene was added to the reagent (0·01 per cent) before addition of the sample to block any further lipid peroxidation. The reaction was carried out at 100°C for 25 min, after which time the supernatant was obtained by centrifugation. The absorbance of the supernatant was measured at a wavelength of 535 nm against a reagent blank.

Statistical analysis

Between-group results were analysed with Wilcoxon's rank sum test. Within-group trends were analysed with Wilcoxon's signed rank test for paired data. $P \leq 0·05$ was considered significant.

Results

All patients recovered fully with salvaged limbs; all bypasses were patent on duplex scanning 5–7 days after surgery. There was no significant difference between median clamp times for groups 1 and 2 (17 (range 12–23) *versus* 15 (range 11–28) min respectively).

Preclamp indices

Before revascularization, median xanthine oxidase activity in femoral vein blood was significantly greater in group 1 (1·45 nmol min^{-1} ml^{-1}) than in group 2 (less than 0·10 nmol min^{-1} ml^{-1}) ($P<0·01$) or group 3 (less than 0·10 nmol min^{-1} ml^{-1}) ($P<0·01$) (*Table 1*). Preclamp xanthine oxidase activity in group 2 did not differ significantly from that in the control group. Concomitant estimation in groups 1, 2 and 3 of conjugated diene levels (median 1·04, 0·85 and 0·88 respectively) and of malondialdehyde concentration (median 0·03, 0·03 and 0·02 respectively) (*Table 1*) failed to show any differences between the three groups, nor were there any differences in creatine kinase, K^+, or creatinine concentrations (*Table 2*).

Seven of the nine patients with a preclamp ABPI lower than 0·4 had a preclamp xanthine oxidase activity greater than 0·9 nmol min^{-1} ml^{-1}. This was significantly greater ($P<0·01$) than preclamp xanthine oxidase activity when the ABPI was higher than 0·4. Eight patients had a preclamp xanthine oxidase activity of less than 0·1 nmol min^{-1} ml^{-1}, their ABPI measurement ranging from 0·4 to 0·9 (median 0·6) (*Fig. 1*).

Postclamp indices

Patients in groups 1 and 2 showed a significant increase ($P<0·01$) in median xanthine oxidase activity in femoral vein blood 2 min after clamp release (3·49 and 5·89 nmol min^{-1} ml^{-1} respectively), compared with preclamp levels. At 60 min after clamp release, median xanthine oxidase activity in group 1 (1·77 nmol min^{-1} ml^{-1}) and group 2 (2·30 nmol min^{-1} ml^{-1}) had decreased ($P<0·01$ and $P<0·01$ respectively) compared with 2-min levels, but both were still significantly higher than the preclamp value ($P<0·01$). There were no significant differences in xanthine oxidase activity between groups 1 and 2, at 2 or 60 min after clamp release (*Table 1*).

In contrast to the changes in xanthine oxidase activity, the concentration of conjugated dienes in both groups 1 and 2 fell significantly 2 min after clamp release ($P<0·01$), then showed no change between 2 and 60 min (*Table 1*). However, the trend for conjugated dienes was

Table 1 Activity of xanthine oxidase and levels of conjugated dienes and malondialdehyde before and during reperfusion in patients with critical ischaemia, claudicants and controls

	Before clamping	Reperfusion		
		2 min	20 min	60 min
Xanthine oxidase (nmol min^{-1} ml^{-1})				
Ischaemics	1·45 (1·06–2·12)*	3·49 (3·10–12·71)†	2·12 (1·70–2·12)‡	1·77 (0·50–3·88)§
Claudicants	<0·1 (<0·1 to <0·1)	5·89 (4·24–14·31)†	3·90 (1·70–5·09)‡	2·30 (1·30–3·81)§
Controls	<0·1 (<0·1 to <0·1)	—	—	—
Conjugated dienes (absorption at 233 nm)				
Ischaemics	1·04 (0·86–1·13)	0·81 (0·77–0·95)†	0·79 (0·75–0·83)	0·79 (0·77–0·93)
Claudicants	0·85 (0·81–1·13)	0·75 (0·72–0·94)†	0·71 (0·64–0·81)	0·84 (0·74–0·89)
Controls	0·88 (0·74–1·00)	—	—	—
Malondialdehyde (absorption at 535 nm)				
Ischaemics	0·03 (0·03–0·08)	0·02 (0·02–0·08)	0·02 (0·02–0·03)	0·02 (0·02–0·06)
Claudicants	0·03 (0·02–0·04)	0·03 (0·02–0·04)	0·04 (0·02–0·06)	0·02 (0·01–0·05)
Controls	0·02 (0·01–0·04)	—	—	—

Values are median (interquartile range). *$P<0·01$ *versus* claudicants and controls; †$P<0·01$ *versus* preclamp value; ‡$P<0·05$ *versus* 2 min reperfusion; §$P<0·01$ *versus* 2 min reperfusion and preclamp values (Wilcoxon test)

Table 2 Levels of creatine kinase, potassium and creatinine before and during reperfusion in patients with critical ischaemia, claudicants and controls

	Before clamping	Reperfusion		
		2 min	20 min	60 min
Creatine kinase (units l^{-1})				
Ischaemics	135 (62–182)	97 (55–332)	109 (59–178)	123 (67–237)
Claudicants	87 (39–201)	87 (46–194)	81 (39–130)	101 (82–189)
Controls	118 (60–136)	—	—	—
Potassium (mmol l^{-1})				
Ischaemics	4·6 (4·2–5·7)	4·3 (3·9–5·3)	4·7 (3·8–5·2)	4·6 (4·4–5·3)
Claudicants	4·2 (3·9–4·3)	4·2 (4·1–4·4)	4·3 (4·0–4·6)	4·4 (3·9–4·6)
Controls	3·7 (3·6–4·0)	—	—	—
Creatinine (μmol l^{-1})				
Ischaemics	119 (81–133)	128 (77–291)	107 (78–132)	123 (76–133)
Claudicants	95 (75–98)	79 (69–95)	86 (76–103)	92 (70–99)
Controls	85 (81–103)	—	—	—

Values are median (interquartile range). There were no significant differences between the three groups

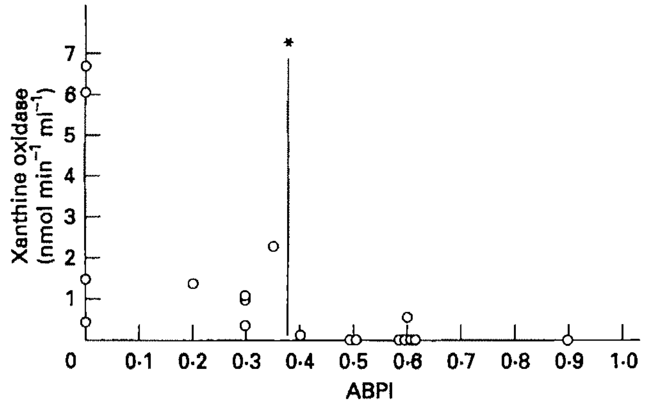

Fig. 1 Preoperative ankle: brachial pressure index (ABPI) *versus* preclamp xanthine oxidase activity in ten claudicants and eight patients with critical ischaemia. $^*P<0·01$ (ABPI $\leq 0·39$ *versus* ABPI $\geq 0·4$, Wilcoxon test)

Table 3 Xanthine oxidase activity in femoral and brachial veins before clamping and 20 min after release of femoral vein clamp

	Xanthine oxidase (nmol min^{-1} ml^{-1})	
	Before clamping	20 min reperfusion
Femoral vein	1·01 (0·55–1·68)*	1·91 (1·08–2·10)
Brachial vein	2·87 (0·63–3·59)	2·01 (0·97–2·95)

Values are median (interquartile range). $^*P<0·01$ (femoral *versus* brachial vein, Wilcoxon test)

not seen in malondialdehyde levels, which did not change throughout the monitored period.

Plasma K^+ and creatinine concentrations, and creatine kinase activity were unchanged in either group during the 60-min period (*Table 2*). There was no clinical or biochemical evidence of muscle damage or renal failure in any patient during this time.

Brachial vein samples

In group 1, median xanthine oxidase activity in preoperative brachial vein blood was greater ($P<0·01$) than in femoral vein blood (2·87 *versus* 1·01 nmol min^{-1} ml^{-1} respectively) (*Table 3*). At 20 min after release of clamps there was no difference between brachial and femoral vein xanthine oxidase activities (median 2·01 and 1·91 nmol min^{-1} ml^{-1} respectively). There was no significant difference in the levels of conjugated dienes and malondialdehyde between arm and leg samples at any time point.

Discussion

This study shows that xanthine oxidase may be induced before revascularization. The high preclamp levels appear to be related to the degree of ischaemia as indicated by the clinical evaluation and the ABPI measurement.

Nuclear magnetic resonance (NMR) spectroscopy[10] has shown that ischaemia is associated with alterations in phosphate metabolite levels in the affected muscle, which are relatively mild, and these changes are not simply related to ABPI. It was suggested that an ABPI greater than 0·4 is sufficient to maintain metabolite levels above a critical level, lessening the risk of reperfusion injury, but below this threshold metabolite levels cannot be maintained. Other studies have shown that a high degree of ischaemia is necessary for muscle damage to occur[11] and that the duration of ischaemia is related to the extent of muscle damage[1].

As indicated by conjugated dienes, malondialdehyde, creatine kinase and K^+ measurements, the preoperative rise in xanthine oxidase activity in critical ischaemia is not accompanied by lipid peroxidation. Histological studies of prereperfusion of ischaemic muscle[11] support this finding. It is generally accepted that the assays employed to assess the levels of conjugated dienes and malondialdehyde are rather non-specific in biological fluids; however, the authors believe the within-patient trends shown by these tests give a valid reflection of biochemical events, although patient-to-patient comparisons are less valid.

After revascularization both groups showed a significant increase in xanthine oxidase activity, peaking at 2 min, then returning to near normal levels by 60 min, although still raised slightly. This finding is consistent with the findings of Punch *et al.*[12], who investigated ischaemic rat hind limbs and found that xanthine oxidase activity in venous effluent increased fourfold compared with preischaemia levels, 5 min after reperfusion, and subsequently decreased to near preischaemia levels at 15 min. Their study also showed that rat plasma xanthine oxidase activity increased to higher levels after 4 h than after 2 h ischaemia. A similar phenomenon was suggested by Friedl *et al.*[13] in experimental human models. However, this was not a finding of the present study, there being no statistical difference between peak xanthine oxidase activity in patients with critical ischaemia and rest pain and in intermittent claudicants with no rest pain.

Collateral circulation may explain the raised preoperative xanthine oxidase activity in patients in group 1. Complete ischaemia with no circulation, e.g. 4-h tourniquet application, is not sufficient to raise xanthine oxidase activity above normal levels before revascularization[12], nor is ischaemia on effort with only collateral circulation (group 2). The combination of severe ischaemia with collateral circulation may result in biochemical changes similar to those seen in reperfusion injury syndrome. Evidence of the involvement of collateral circulation is also given by NMR studies[10], which showed that metabolic changes (i.e. a high inorganic phosphate:phosphocreatine ratio) in patients with acute ischaemia were relatively mild. The collateral circulation is thought to maintain muscle metabolite levels above a critical level.

Before operation xanthine oxidase was the only variable measured that showed any significant difference between patients with critical ischaemia and those with intermittent claudication. This finding suggests the potential of xanthine oxidase as a biochemical marker, not of critical ischaemia alone, but of the sufficiency of the collateral circulation in critical ischaemia.

The finding of xanthine oxidase in the general circulation before revascularization led the authors to conclude that collateral circulation is evident in critical ischaemia and in this experiment was responsible for the leakage of xanthine oxidase from the ischaemic limb to the rest of the circulation. Of interest, systemic levels of xanthine oxidase were greater than ischaemic limb vein levels. This finding is hard to explain. Accumulation of xanthine oxidase in the systemic circulation before revascularization on its own would not explain the phenomenon, as similar levels would be expected in brachial and femoral samples if xanthine oxidase is not destroyed or added in the systemic circulation.

The products of lipid peroxidation did not increase during the study period. Indeed, concentrations of conjugated dienes fell significantly 2 min after clamp release, a finding the authors cannot explain. It is concluded that, if lipid peroxidation does occur, it does so some time after the first 60 min of reperfusion when the xanthine oxidase activity has returned to normal levels. In acute ischaemia, sequential measurements of myoglobin as a marker of rhabdomyolysis[11] have shown peak levels indicating maximal activity to be hours rather than minutes after successful revascularization. Furthermore, in the present study there were no cases of acute ischaemia and no evidence of muscle injury in the first 60 min on biochemical grounds. The authors suggest that xanthine oxidase-generated free radicals cause little or no tissue damage in chronic ischaemia during the early phase of reperfusion injury syndrome, even though superoxide radical scavengers have been shown to reduce the damage caused by reperfusion injury[5]. The present study suggests that free radicals generated by xanthine oxidase are not the primary cause of tissue damage, but may be intermediaries in a more complex process that culminates in the muscle breakdown seen in reperfusion injury syndrome.

The comprehensive review by Grace[1] reveals a host of possible routes from the appearance of xanthine oxidase to lipid peroxidation. The induction of xanthine oxidase, although of little direct consequence, appears to trigger a cascade of systems of greater destructive potential, which continue to exert their influence long after their stimuli have disappeared.

It is concluded that reperfusion injury syndrome has a triphasic nature. The present study provides evidence for the first two phases, i.e. the ischaemic and early reperfusion phases (2–5 min after revascularization), during which time superoxide radicals are generated but very little, if any, muscle damage occurs. The third phase (late reperfusion injury) occurs hours after revascularization when biochemically and histologically demonstrable muscle damage occurs. The finding of detectable levels of xanthine oxidase in critical ischaemia before revascularization points to a potentially valuable role in diagnosis. Of interest is the discovery that xanthine oxidase activity is intense but short lived following clamp release after revascularization for critical ischaemia and claudication. Finally, the authors report the interesting but inexplicable finding of systemic (brachial) vein levels of xanthine oxidase activity greater than those in the main limb-draining vein (femoral) in critical ischaemia before revascularization.

Acknowledgements

The authors thank the technical staff of the Department of Chemical Pathology for assistance in sample processing. The expert advice and guidance of Dr David Jones from the Department of Physiology were greatly appreciated.

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British Journal of Surgery 1996, 83, 803–809

Experimental application of controlled limb reperfusion after incomplete ischaemia

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Severe local and systemic complications may occur after revascularization of extremities exposed to prolonged complete or incomplete ischaemia. These complications may be reduced by controlling the reperfusate and the circumstances of the reperfusion period. Ten adult German domestic pigs were exposed to 6 h of incomplete limb ischaemia by occlusion of the left iliac artery. To simulate the clinical situation of embolectomy, the occlusive snares were released after the ischaemic period in five pigs and normal blood flow developed with systemic pressure (uncontrolled reperfusion). In the other five pigs, a controlled reperfusate was delivered at controlled pressure before establishing normal blood reperfusion (controlled reperfusion). At the end of the observation period (90 min after start of reperfusion), the group with controlled reperfusion had a lower mean(s.e.m.) tissue water content (81·8(0·7) *versus* 84·3(0·7) per cent, $P < 0{\cdot}05$, a greater increase in tissue adenosine $5'$-triphosphate compared with values at the end of ischaemia (6·2(1·5) *versus* −2·5(1·8) µmol per g protein, $P < 0{\cdot}03$), a higher tissue pH (7·2(0·1) *versus* 6·8(0·1), $P < 0{\cdot}03$), a smaller temperature decrease (0·3(0·2) *versus* 1·2(0·3)°C, $P < 0{\cdot}05$), lower concentrations of creatine kinase (355·0(87·5) *versus* 624·4(73·4) units/l, $P < 0{\cdot}05$) and lactate dehydrogenase (LDH) (369·5(42·5) *versus* 538·4(39·2 units/l, $P < 0{\cdot}03$) in the femoral vein blood and lower LDH concentrations (356·5(48·9) *versus* 546·0(37·8 units/l, $P < 0{\cdot}03$) in central venous blood. These data indicate that severe local and systemic damage occurs with uncontrolled (normal blood) reperfusion even after incomplete limb ischaemia, and that these changes can be reduced by delivering a controlled reperfusate under controlled conditions.

Normal blood reperfusion after revascularization following prolonged limb ischaemia is associated with systemic complications and severe local damage. In patients, mortality rates vary between 14 and 68 per cent and amputation rates between 6 and 31 per cent[1–4]. Even after successful revascularization, good functional recovery occurs in only 60–70 per cent of survivors, while one-third of patients have a viable, but non-functioning extremity[5]. This is a result of the reperfusion syndrome originally described by Haimovici[6] in 1960. The syndrome is characterized by a high efflux of potassium, creatine phosphokinase, lactate, toxins and myoglobin. The developing metabolic changes (hyperkalaemia, acidosis) may cause severe cardiac depression with arrhythmias, low cardiac output or even death[7]. Cell swelling, oedema, release of toxin and myoglobin in combination with hypovolaemia, haemoconcentration and circulatory depression or shock may lead to renal (anuria), pulmonary (adult respiratory distress syndrome (ARDS), lung oedema) and hepatic failure[8]. Skeletal muscle is relatively resistant to ischaemia and there is still structural integrity even after prolonged ischaemia[9]. With the onset of normal blood reperfusion, additional damage occurs to the energy-depleted muscle cell[10]. In addition to cell swelling and acidosis, depletion of adenine nucleotide precursors, free radical production and calcium overload have been proposed as responsible mechanisms[11]. Primary amputation of an ischaemic limb lowers mortality by avoiding reperfusion syndrome[12]. The goal of therapy should be to avoid the development of reperfusion damage instead of treatment after it has occurred. Major progress has been made in open heart surgery to diminish damage after prolonged coronary occlusion by controlling the circumstances of the initial reperfusion period[13–15]. No such concept exists for protection of ischaemic skeletal muscle, even though extremity ischaemia is a major clinical problem. Previous studies have shown that intervention during the initial reperfusion phase after prolonged limb ischaemia reduces the severity of complications[9,11,16–18]. Furthermore, the superiority of controlled limb reperfusion over normal blood reperfusion has been demonstrated in a pig model with 6 h of infrarenal aortic occlusion[16] and in clinical studies in patients with prolonged total limb ischaemia[17,18]. In clinical practice, however, ischaemia is often incomplete and it is difficult to determine time and severity of ischaemia, pre-existing damage and the possible result following normal blood reperfusion. This study was designed to test the hypothesis that controlled reperfusion is also beneficial and safe when applied after prolonged incomplete limb ischaemia.

Materials and methods

Preparation of animals

Ten German domestic pigs aged between 20 and 25 weeks and weighing between 45 and 50 kg were used. The pigs were anaesthetized with ketamine hydrochloride 10 mg/kg and chlorhydrate 5,6-dihydro-2-(2,6-xylidino)-4H-1,3-thiazine 2 mg/kg intramuscularly, and metomidathydrochloride 100–150 mg intravenously. Anaesthesia was maintained with pentobarbital sodium 6–20 mg/min intravenously. All animals received humane care in compliance with the guidelines of the National Institutes of Health[19]. After endotracheal intubation, positive-pressure ventilation with 30 per cent oxygen was delivered with a Stephan

Presented to the 4th European Congress of Surgery (Eurosurgery 94), in Berlin, Germany, October 1994
Paper accepted 2 September 1995

Respirator (Stephan, Quickborn, Germany). Polyethylene catheters were placed into the left carotid artery and connected to a recorder (Digital Display; Gould, Cleveland, Ohio, USA) for monitoring systemic blood pressure, heart rate and for blood gas analyses. Catheters were also put into both jugular veins for drawing venous blood, to give infusions and to measure central venous pressure. A Swan-Ganz (Cardiac output computer, HMV 7905, Hoyer, Bremen, Germany) catheter was installed into the outlet of the right ventricle to measure cardiac output. The left iliac artery and vein were prepared extraperitoneally after a lower left pararectal incision. The artery was armed with rubber snares and an electromagnetic blood flow transducer. A polyethylene catheter was placed into the femoral vein to draw venous blood and monitor venous pressure.

Experimental groups

The clinical situation of embolism/embolectomy was simulated in five pigs by occluding the left iliac artery with rubber snares and reperfusing with normal blood at systemic pressure (uncontrolled reperfusion) after 6 h of incomplete ischaemia of the limb. In the other five pigs, the left iliac artery was also occluded for 6 h. Before re-establishing normal blood flow, the proximal iliac artery was cannulated with a 12-Fr cannula (Bard, Irvine, California, USA) and the distal iliac artery with a 10-Fr cannula. The cannulas were connected with a roller pump (Stöckert, München, Germany) and a heat exchanger via a reperfusion set (HP-Medica, Augsburg, Germany). After systemic heparinization with 300 units per kg body-weight, blood was withdrawn from the proximal iliac artery and modified with a crystalloid reperfusion solution (*Table 1*) in a ratio of 6 : 1 (blood : solution). Controlled limb reperfusion was performed for 30 min at a pressure less than or equal to 50 mmHg and at a temperature of 37°C. Thereafter, the iliac artery was decannulated, the arteriotomy closed, the occlusive snares released and normal blood flow re-established. After the reperfusion period, the animals in both groups were observed for a further 60 min before final measurements were taken (90 min after start of reperfusion).

Measured variables

Blood parameters. Potassium and calcium were analysed with a Gem-Stat Blood Analyser (Mallinckrod, Hennef/Sieg, Germany). Haematocrit, haemoglobin, oxygen pressure (pO_2) and pH were measured with an AVL 947 automatic blood gas system (AVL, Bad Homburg, Germany). Creatine kinase (CK), lactate dehydrogenase (LDH) and glucose were determined with a random access analyser (Hitachi 717; Boehringer, Mannheim, Germany). At baseline no additional blood sample was drawn from the femoral vein. The values from central venous blood alone were used.

Blood flow. Blood flow in the iliac artery was measured using an electromagnetic flowprobe (Flow-Probe SP7515; Statham, Cleveland, Ohio, USA) and recorded by a flowmeter (SP2202; Statham).

Table 1 Composition of reperfusate solution

Component	Volume (ml)	Concentration	Principle
Glucose (10%)	315	330–340 mg%	Supply substrate, reduce oedema, increase osmolarity
Citrate-phosphate-dextrose	270	Calcium 1·5 mmol/l	Reduce calcium overload
Glutamate and aspartate	450	13 mmol/l each	Supply substrate
Thromethamine	36	pH 7·5–7·6	Buffer acidosis
Allopurinol	2·5	100 mg total dose	Scavenge oxygen free radicals

Muscle water content. Water content in the skeletal muscle (tibialis anterior) was measured by weighing a muscle biopsy of 1–2 kg before and after freeze-drying in a vacuum lyophilizer (Freeze Dryer Moduluo; Edwards, Crawley, UK) at −50°C for 48 h.

Muscle temperature and pH. Temperature in the limb muscle (tibialis anterior) was recorded by means of a temperature probe (Myocardial temperature sensor; Sims, California, USA) connected to a temperature recorder (Tastoterm D 700; Impact, Hanau, Germany). A precalibrated, 21-G stainless steel electrode (Ingold Elektrode U-402-M3; Ingold, Steinbach, Germany) was inserted in the muscle close to the temperature probe and connected to a pH-meter (Digital pH-Meter; Knick, Berlin, Germany) in order to measure muscle pH.

Muscle adenosine 5′-triphosphate. A Tru-Cut (Travenol Laboratories, Deerfield, Illinois, USA) needle was used to take muscle biopsies from the tibial muscle. The samples were quick-frozen in liquid nitrogen and homogenized together with 500 µl perchlorate and 4 mmol ethylenediamine tetra-acetic acid. Before centrifugation, 80 mg Tris was added and a small part separated to measure protein. Protein was analysed by means of the biuret method (Merckotest-Total-Protein; Merck, Darmstadt, Germany). Adenosine 5′-triphosphate (ATP) was determined by the luciferin–luciferase reaction according to Lundin and co-workers[20]. The values were expressed relative to the protein content of the biopsy (µmol per protein).

Calculated variables

Oxygen and glucose consumption. Oxygen consumption (VO_2) was calculated as:

$$VO_2 \text{ (ml per 100 g per min)} = \text{arterial–venous } O_2 \text{ difference} \times \text{flow}$$

Glucose consumption was determined using the formula:

$$\text{Glucose consumption (mg per 100 g per min)} = \text{arterial–venous glucose difference} \times \text{flow}$$

Flow in the limb. Flow in the limb was calculated using the formula:

$$\text{Flow (ml per 100 g per min)} = (\text{flow in the iliac artery/limb weight}) \times 100$$

Vascular resistance. Vascular resistance (VR) was assessed as:

$$\text{VR (dynes} \times \text{s per cm}^5) = (\text{MAP} - \text{VP}) \times 80/\text{flow}$$

where MAP is mean arterial pressure (mmHg), VP is venous pressure (mmHg; iliac vein), 80 is the constant and flow is the flow in the iliac artery in ml/min.

Water content. Tissue water content was calculated according to the following equation:

$$\% \text{ water} = \text{wet weight} - \text{dry tissue weight} \times 100/\text{wet tissue weight}$$

Measuring times

The following measurements were made before ischaemia (baseline), after 6 h of ischaemia and 90 min after reperfusion: limb tissue water content, ATP content, pH and temperature. All other measurements were done at 5, 30 and 60 min of reperfusion in addition to the abovementioned times. Flow in the iliac artery, flow in the limb, oxygen and glucose consumption were not determined at the end of ischaemia.

Statistical analysis

Statistical analysis was done in cooperation with the statistical department of the Albert-Ludwigs-University of Freiburg, Germany. Data were analysed with StatView V2.0 (Abacus Concepts, Berkeley, California, USA) on a Macintosh IICi com-

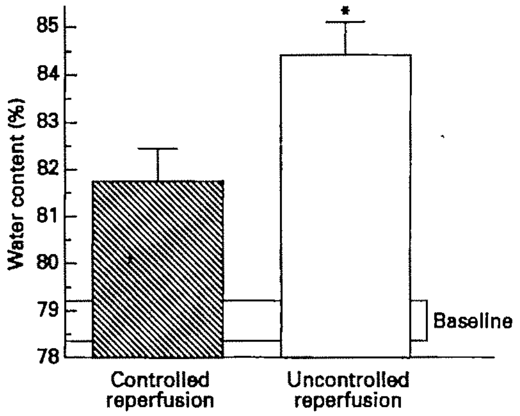

Fig. 1 Water content in the limb muscle before (baseline) and after (reperfusion 90 min) 6 h of incomplete ischaemia followed by controlled reperfusion (▨) and uncontrolled (☐) reperfusion. *$P<0·05$ *versus* controlled reperfusion

Table 2 Oxygen and glucose consumption before and during controlled or uncontrolled reperfusion

	Controlled reperfusion ($n=5$)	Uncontrolled reperfusion ($n=5$)
Oxygen consumption (ml per 100 g per min)		
Baseline		
Reperfusion (min)	11·3(2·2)	12·3(3·1)
5	32·7(3·4)†	15·8(1·9)
30	29·1(4·9)*	13·4(3·3)
60	14·8(1·8)	16·9(2·7)
90	14·1(1·5)	18·7(2·1)
Glucose consumption (mg per 100 g per min)		
Baseline		
Reperfusion (min)	21·0(8·8)	20·0(5·3)
5	439·0(115·7)*	16·5(4·7)
30	289·1(91·2)*	19·0(5·2)
60	35·6(17·8)	10·7(2·1)
90	12·2(2·9)	14·2(5·5)

Values are mean(s.e.m.). *$P<0·03$; †$P<0·01$ *versus* uncontrolled reperfusion

puter (Apple, Cupertino, California, USA). Analysis of variance was employed for overall comparison. Differences between individual groups were evaluated by *t* test and by Scheffe *F* test. The paired two-tail Student's *t* test was used for comparison of repeatedly documented variables within experimental groups. Differences were considered significant at a probability level of $P<0·05$. Group data are expressed as mean(s.e.m.).

Results

Changes during ischaemia

There were no differences between the two groups in any of the studied parameters at baseline or after 6 h of ischaemia. Haemodynamic parameters remained stable during the ischaemic period. Ischaemia caused a drop in mean(s.e.m.) pH of 0·77(0·1) or 12 per cent ($P<0·0003$) in the muscle and 0·12(0·04) ($P<0·001$) in femoral vein blood, compared with baseline values. Mean(s.e.m.) muscle temperature dropped 8 per cent (2·9(0·5)°C; $P<0·003$) and mean(s.e.m.) muscle ATP fell 18·6(1·5) µmol per g protein (60 per cent; $P<0·003$). Systemic venous glucose levels decreased 53 per cent (48·1(6·6) mg/dl; $P<0·001$), CK levels increased 171 per cent (217·4(67·8) units/l; $P<0·03$) and LDH increased 41·7(19·4) units/l. In femoral vein blood, CK increased 230·8(70·4) units/l (176 per cent; $P<0·03$) and LDH levels at the end of ischaemia were 34·0(25·6) units/l higher than at baseline (*P* not significant).

Table 3 Limb muscle adenosine 5′-triphosphate, pH and temperature before, after 6 h of incomplete ischaemia, at the end of reperfusion and the difference between baseline and the end of reperfusion values

	Controlled reperfusion ($n=5$)	Uncontrolled reperfusion ($n=5$)
ATP (µmol per g protein)		
Baseline	31·3(1·3)	26·3(4·9)
End of ischaemia	10·9(1·3)	12·2(2·5)
Reperfusion 90 min	17·0(2·4)	9·7(4·3)
Decrease	14·3(1·8)	16·6(0·6)
pH		
Baseline	7·4(0·1)	7·4(0·1)
End of ischaemia	6·7(0·2)	6·5(0·1)
Reperfusion 90 min	7·2(0·1)†	6·8(0·1)
Decrease	0·2(0·1)*	0·6(0·1)‡
Temperature (°C)		
Baseline	35·6(0·3)	36·2(0·3)
End of ischaemia	32·9(0·7)	33·0(0·7)
Reperfusion 90 min	35·0(0·2)	35·3(0·4)
Decrease	0·3(0·2)*	1·2(0·3)§

Values are mean(s.e.m.). ATP, adenosine 5′-triphosphate. *$P<0·05$, †$P<0·03$ *versus* uncontrolled reperfusion; ‡$P<0·05$, §$P<0·001$ *versus* controlled reperfusion

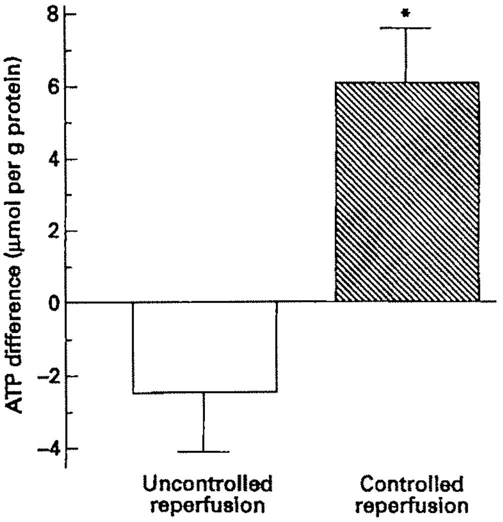

Fig. 2 Recovery of muscle adenosine 5′-triphosphate (ATP) expressed as the difference in ATP between end of ischaemia and end of reperfusion values after controlled (▨) and uncontrolled (☐) reperfusion. Note the increase after controlled reperfusion and the further decrease after uncontrolled reperfusion. *$P<0·03$ *versus* uncontrolled reperfusion

Changes during reperfusion

Oxygen and glucose consumption. Data are shown in

Table 2. During the initial reperfusion phase the group which had controlled reperfusion showed significantly higher oxygen consumption after 5 min of reperfusion ($P<0\cdot01$) and after 30 min of reperfusion ($P<0\cdot03$), as well as higher glucose consumption compared with the animals which had uncontrolled reperfusion. No differences were noted at baseline or during the reperfusion period.

Water content, muscle ATP, pH and temperature. Data are shown in *Table 3* and *Figs 1* and *2*. There was a significantly lower water content after controlled as compared to uncontrolled reperfusion (*Fig. 1*). At the end of the observation period (90 min after start of reperfusion), pigs with controlled reperfusion had higher muscle ATP levels than the animals without controlled reperfusion (*P* not significant). Both groups showed a similar ATP reduction from baseline. The beneficial effect of controlled reperfusion could be seen in the difference between the ATP levels at the end of ischaemia and the end of observation. A further reduction in ATP levels was observed during uncontrolled reperfusion, whereas animals which had controlled reperfusion showed a significant ($P<0\cdot03$) increase in muscle ATP levels (*Fig. 2*).

During controlled reperfusion there was a significant improvement in muscle pH compared with levels at the end of ischaemia ($P<0\cdot05$) in contrast to the animals with uncontrolled reperfusion, where pH increased only slightly. At the end of the observation period (90 min) pH was higher in animals given controlled reperfusion ($P<0\cdot03$), whereas the uncontrolled group remained severely acidotic. Compared with baseline levels there was only a small reduction in muscle pH in the controlled reperfusion animals ($P<0\cdot05$ compared with uncontrolled reperfusion group). In contrast, the group with uncontrolled reperfusion showed a significant reduction in muscle pH to a severely acidotic level ($P<0\cdot001$ compared with baseline).

The absolute muscle temperature was comparable between the groups. The animals treated with controlled reperfusion showed only a minor decrease in temperature (compared with baseline levels) at the end of the observation period (90 min), whereas the untreated animals exhibited a much higher temperature reduction ($P<0\cdot001$).

Potassium, CK and LDH. Data are shown in *Table 4* and *Figs. 3* and *4*. Potassium was lower in the controlled reperfusion group, but the decrease only reached significance ($P<0\cdot005$) at the end of the observation period (90 min). All potassium levels during reperfusion in the uncontrolled group were higher than at baseline, the highest levels being observed at the time of the initial reperfusion (5 min).

Compared with levels at the end of ischaemia, there was a significant reduction in systemic LDH during initial reperfusion (5 min) in the group with controlled reperfusion ($P<0\cdot05$), whereas the animals with uncontrolled reperfusion showed an increase ($P<0\cdot003$ in comparison between groups). Throughout the rest of the reperfusion

Table 4 Potassium and lactate dehydrogenase in the femoral vein blood and creatine kinase in the systemic venous blood before, after 6 h of incomplete ischaemia and during controlled or uncontrolled reperfusion

	Controlled reperfusion ($n=5$)	Uncontrolled reperfusion ($n=5$)
Potassium (mmol/l)		
Baseline	4·5(0·3)	4·1(0·1)
End of ischaemia	4·5(0·4)	4·7(0·1)
Reperfusion (min)		
5	4·0(0·5)	5·0(0·3)
30	4·1(0·4)	4·9(0·5)
60	3·8(0·4)	4·6(0·1)
90	3·7(0·1)‡	4·5(0·1)
Lactate dehydrogenase (units/l)		
Baseline	429·2(75·8)	568·2(21·3)
End of ischaemia	560·0(106·8)	598·6(22·1)
Reperfusion (min)		
5	286·2(38·2)#¶	604·6(30·7)
30	319·7 (42·1)‡	571·8(38·0)
60	340·0(23·3)§	544·2(34·5)
90	369·5(42·5)†	538·4(39·2)
Creatinine kinase (units/l)		
Baseline	336·0(66·6)	275·2(32·6)
End of ischaemia	495·8(136·8)	550·2(69·7)
Difference (min)		
5	− 100·4(38·0)*	65·2(28·6)
30	− 143·7(87·3)*	64·4(36·8)
60	− 95·2(51·6)*	41·2(27·7)
90	− 47·0(37·9)*	51·6(26·9)

Values are mean(s.e.m.). $^*P<0\cdot05$, $^{\dagger}P<0\cdot03$, $^{\ddagger}P<0\cdot005$, $^{\S}P<0\cdot003$, $^{\#}P<0\cdot0003$ *versus* uncontrolled reperfusion and $^{\P}P<0\cdot05$ *versus* end of ischaemia

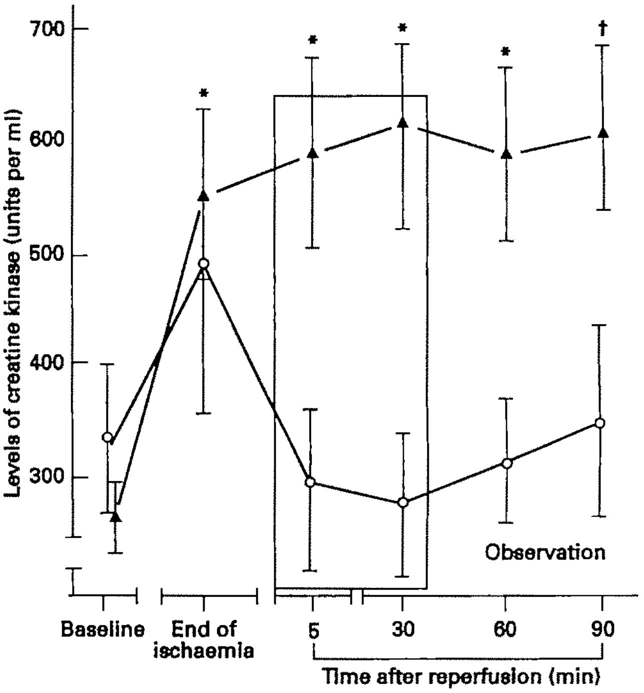

Fig. 3 Levels of creatine kinase in femoral vein blood before ischaemia (baseline), after 6 h of incomplete ischaemia (end of ischaemia), during controlled (O) and uncontrolled (▲) reperfusion (5 and 30 min), and after reperfusion (60 and 90 min; observation). Note the persistent high levels after uncontrolled reperfusion. $^*P<0\cdot03$, $^{\dagger}P<0\cdot05$ *versus* controlled reperfusion

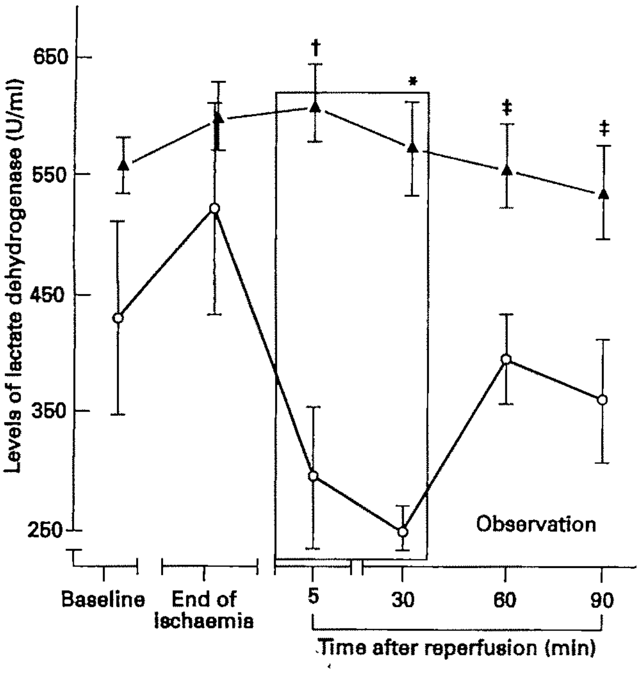

Fig. 4 Levels of lactate dehydrogenase in systemic venous blood before ischaemia (baseline), after 6 h of incomplete ischaemia (end of ischaemia), during controlled (O) and uncontrolled (▲) reperfusion (5 and 30 min) and after reperfusion (60 and 90 min; observation). Note the persistent high levels after uncontrolled reperfusion. $^*P<0·0003$, $^†P<0·003$, $^‡P<0·03$ *versus* controlled reperfusion

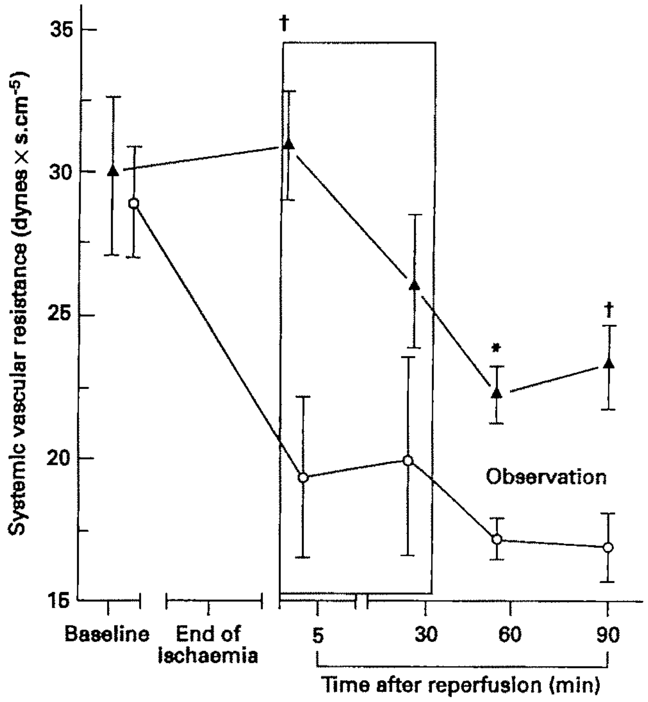

Fig. 5 Systemic vascular resistance in the limb before 6 h of incomplete ischaemia (baseline) and during (5, 30, 60 and 90 min) controlled (O) and uncontrolled (▲) reperfusion. $^*P<0·01$, $^†P<0·03$ *versus* controlled reperfusion

period, systemic and femoral vein LDH were much higher in the animals with uncontrolled reperfusion than in those with controlled reperfusion ($P<0·005$, $P<0·003$ and $P<0·03$). The levels of CK in the femoral vein are presented in *Fig. 3*. There were significantly higher levels of CK in the group with uncontrolled reperfusion during the reperfusion period, whereas a reduction in CK (compared with the end of ischaemia) was observed in the group with controlled reperfusion. Systemic CK values are shown in *Table 4*.

Flow and haemodynamics. In the animals which had controlled reperfusion, mean(s.e.m.) flow in the iliac artery was slightly increased at 30 min of reperfusion (275(48) *versus* 260(38) ml/min; P not significant) and was at baseline level (257(41) ml/min) at the end of the observation period (90 min). During uncontrolled reperfusion there was a decrease in iliac flow at all times of reperfusion, reaching significance ($P<0·0005$) at 5 min of reperfusion (196(9) *versus* 300(3) ml/min).

As a result of the high individual variation in arterial flow in the iliac artery, there was no difference in flow in the limb between groups. However, compared with baseline levels (5·2(0·1) ml per min per 100 g) there was a significant reduction in mean(s.e.m.) flow in the limb of the uncontrolled reperfusion group at 60 and 90 min (−1·6(0·5) ml per min per 100 g; $P<0·03$ and −1·3(0·4) ml per min per 100 g; $P<0·05$). Controlled reperfusion animals showed only a slight reduction at 60 min (3·9(0·3) *versus* 4·5(0·5) ml per min per 100 g; P not significant) and an improvement in flow in the limb at the end of the observation period (+0·3(0·1) ml per min per 100 g; $P<0·03$). These observations are underlined by the findings for vascular resistance, which were always lower in the group with controlled reperfusion (*Fig. 5*). There were no differences in heart rate, blood pressure or cardiac output between groups (data not shown). The haemodynamic condition of the animals remained stable throughout the ischaemic, reperfusion and observation periods. No side-effects of controlled reperfusion were observed.

Discussion

The results of this clinical *in vivo* model provided biochemical evidence of severe local damage and systemic complications after 6 h of incomplete limb ischaemia if followed by uncontrolled reperfusion (reperfusion injury). Controlled limb reperfusion led to a significant decrease in this reperfusion injury after incomplete ischaemia, resulting in an improved local and systemic status. It confirms former experimental and clinical findings of the beneficial effect of controlled reperfusion after complete limb ischaemia. Furthermore, it stresses former observations that controlled reperfusion is safe and may be suitable for clinical use after prolonged incomplete limb ischaemia.

Systemic and local complications after limb revascularization with normal blood reperfusion after prolonged ischaemia are still frequent regardless of the method of revascularization (surgical or thrombolysis). The complications seen after surgery also develop when reperfusion is initiated by thrombolysis[4,21]. In experimental and clinical studies with controlled reperfusion of ischaemic heart and skeletal muscle, it has been shown that: (1) myocardial salvage is possible, even after periods intact even after 4 h of complete warm limb ischaemia; (3) uncontrolled (normal blood) reperfusion causes severe disruption of the cellular architecture and prevents functional recovery; (4) these deleterious effects of uncontrolled reperfusion can be avoided or reduced by delivering a controlled reperfusate under controlled conditions and (5) functional recovery is possible even after prolonged complete ischaemia[9,11,13,14,16–18]. Theoretically, severe incomplete ischaemia could be worse than complete ischaemia because: (1) a small supply of oxygen to a tissue can result in production of oxygen free radicals, which are extremely reactive to polyunsaturated fatty acids and damage lipid structures in cell membranes[22] and (2) the supply of glucose to the ischaemic tissue can result in anaerobic glycolysis with even higher lactate levels causing a more acidotic pH in the tissue than with complete ischaemia[23]. These points indicate that there are pathophysiological differences in the development of ischaemic and reperfusion damage after incomplete and complete ischaemia. This study was designed to evaluate whether controlled reperfusion has a beneficial effect after 6 h of incomplete limb ischaemia. The superiority of this new concept over uncontrolled reperfusion had already been proven experimentally and clinically after severe complete ischaemia[14,16–18].

The changes caused by ischaemia were typical but less pronounced than after complete ischaemia after aortic occlusion[16]. Muscle temperature, pH and ATP levels were significantly reduced after 6 h in both groups. Increased levels of LDH and CK in the systemic venous blood indicated the presence of effective collateral flow (incomplete ischaemia), as washout of these enzymes occurred. Ischaemia was also confirmed by the changes in femoral vein blood (potassium, CK and LDH increased, glucose and pH reduced). The high CK and especially high LDH levels at baseline and the relatively small increase during ischaemia can be explained by the involvement of a large muscle mass. Despite the long duration of ischaemia, haemodynamic and other blood parameters (haemoglobin, haematocrit pH, pO_2) remained stable (not all data shown), indicating the reliability of the model. This is also confirmed by the stability of a control group without ischaemia[16]. On simulation of the clinical routine of embolectomy, normal blood flow was established after the ischaemic period. This uncontrolled reperfusion method worsened the pre-existing ischaemic damage and resulted in unchanged oxygen metabolism and reduced glucose metabolism (*Table 2*), a further decrease in muscle ATP (*Fig. 2*), a decrease in temperature and persistent tissue acidosis (*Table 3*), oedema (*Fig. 1*) and reduced flow. Furthermore, local and systemic blood levels of CK and LDH remained high, potassium was increased and hypoglycaemia occurred (*Figs 3* and *4*, *Table 4*).

In contrast, the reperfusate itself and the circumstances of the reperfusion were modified in the controlled reperfusion group. The blood withdrawn from the pig aorta was modified by mixing it with a crystalloid reperfusion solution and then delivered with controlled pressure (less than 50 mmHg) for 30 min, before normal blood flow was re-established. The beneficial effect of this controlled reperfusion was seen both locally and systemically. Oxygen and glucose metabolism were significantly improved (*Table 2*), indicating the increased cellular and mitochondrial metabolism necessary for repair mechanisms. During the ischaemic period, pronounced oxygen deficiency developed. The increased oxygen demand during the reparative cell process is reflected in an increase in tissue oxygen extraction during controlled reperfusion[11,18], as confirmed in this model (and that of Mitrev *et al.*[16]). During uncontrolled reperfusion, oxygen uptake is decreased because of mitochondrial and cell damage[11,24]. Additionally, a lack of amino acids occurs during ischaemia[25]. Deamination of glutamate leads to α-ketoglutarate and transamination of aspartate to oxylacetate. Both can enter the Krebs cycle to improve energy production which is necessary for cell repair[15]. Controlled reperfusion with substrate-enriched reperfusate was followed by increased metabolism and resulted in improved ATP levels, increased pH and muscle temperature almost reaching baseline levels. The pathophysiological mechanisms of oxygen and glucose metabolism during controlled and uncontrolled reperfusion are discussed in detail elsewhere[16]. The results of this study indicate that similar changes lead to reduced metabolism after incomplete limb ischaemia. This was circumvented by controlled reperfusion, resulting in improved metabolic response and less injury. Increased glucose metabolism followed by cellular potassium uptake might explain the reduced potassium levels after controlled reperfusion. More severe muscle damage with potassium washout and reduced sodium–potassium pump activity might explain the higher potassium levels after uncontrolled reperfusion[26]. Limb oedema was reduced after controlled reperfusion (*Fig. 1*) by increasing osmolarity of the reperfusate and controlling the reperfusion pressure[11]. Furthermore, flow was also increased during the initial reperfusion period where perfusion was performed with controlled pressure (less than or equal to 50 mmHg). Improved rheology of the reperfusate due to the dilution with crystalloid solution in combination with reduced vascular resistance (*Fig. 5*) may have led to this phenomenon.

No negative effects were observed on the limb or the whole body due to the modification of haemodilution of the reperfusate. Haemodynamic parameters remained stable, systemic values of potassium, calcium, glucose and pH were in the physiological range and levels of CK and LDH were markedly reduced. The explanation that reduced values of enzymes are due to haemodilution is only partly valid. First, the haemodilution reduced haemoglobin and haematocrit by 20–25 per cent (data not shown), whereas CK and LDH were reduced by almost 50 per cent. Second, the haemodilution effect was limited to the first 30 min of reperfusion; there was no difference in haemoglobin and haematocrit between groups at 60 and 90 min (data not shown), but the reduction in CK and LDH remained throughout the whole period. The systemic changes observed in the uncontrolled reperfusion group have the potential for damage especially in elderly patients with reduced cardiopulmonary and renal reserve.

Cellular and mitochondrial calcium overload may lead to mitochondrial dysfunction, followed by impaired cell function, cell death, muscle necrosis and reduced functional recovery[27]. Furthermore, sodium–calcium exchange is depressed under the acidotic conditions that occur with ischaemia[26]. Reactive oxygen metabolites may also play a major part in the microvascular and parenchymal injury to skeletal muscle caused by ischaemia and reperfusion[22,28]. The extent of muscle necrosis is significantly reduced by the administration of free radical scavengers at the onset of reperfusion[29,30]. In addition to mitochondria and activated leucocytes, xanthine oxidase contributes to the production of active oxygen metabolites[26]. It appears likely that allopurinol, which was used in the reperfusion solution, acts as a xanthine oxidase inhibitor as well as a free radical scavenger[31]. Therefore, counteracting acidosis[32], reducing calcium overload[33] and adding a free radical scavenger[30] may have contributed to less cellular injury being observed after controlled reperfusion.

Recently, there has been evidence that the main injury of reperfusion occurs after its onset rather than during the ischaemic period. The contribution of reperfusion to this process has only been appreciated recently[9,11,34,35]. Although reperfusion is necessary for the restoration of metabolic activity, it can also increase the extent of necrosis if it occurs under uncontrolled conditions[36]. This raises the possibility of therapeutic intervention during reperfusion to avoid or reduce this damage. The surgeon is in a unique position, which allows him to control both the composition of the reperfusate and the conditions of reperfusion.

The composition of the reperfusion solution and the conditions of reperfusion (pressure, temperature and duration) stem from previous experience with an *in vitro* rat model[11,27,30,33]. The methods applied in this model warrant investigation in a clinical setting.

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British Journal of Surgery 1996, **83**, 810–811

Case report

Late failure of endoluminal abdominal aortic aneurysm repair due to continued aneurysm expansion

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Endoluminal repair of abdominal aortic aneurysm (AAA) is an alternative to conventional surgery[1]. Reports from several centres[2,3] have demonstrated the feasibility of this technique but its durability remains unknown. This report describes a patient in whom endoluminal grafting failed after 1 year due to progression of the aneurysmal process at the aortic bifurcation. Failure to halt the dilating process may have serious implications for the long-term durability of endoluminal aortic aneurysm repair.

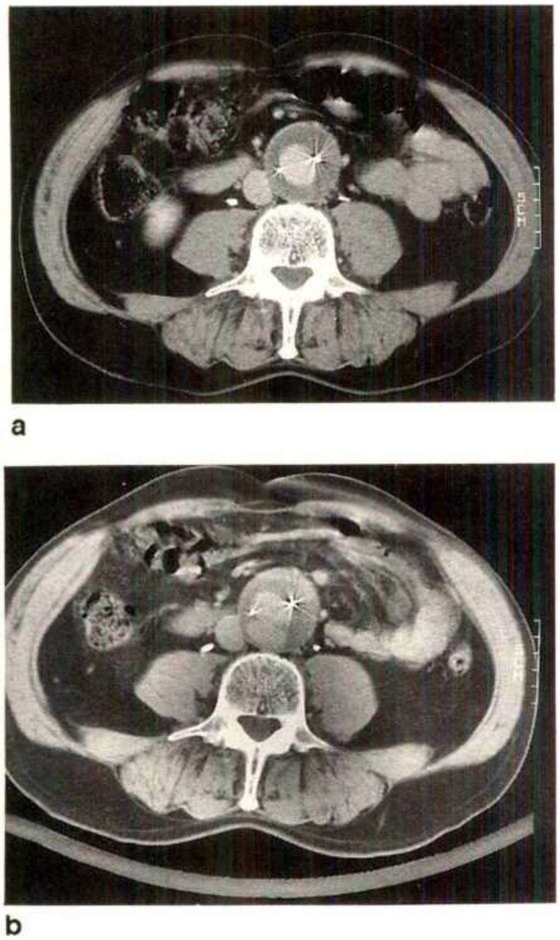

Fig. 1 Contrast-enhanced computed tomography images obtained **a** at 6 weeks after operation showing no evidence of perigraft leak and **b** at 12 months showing a posterior perigraft leak at the distal end

Paper accepted 6 February 1996

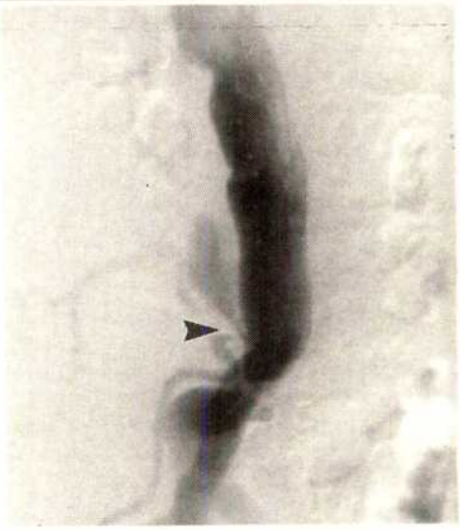

Fig. 2 Intra-arterial digital subtraction angiogram showing a posterior leak at the distal stent site (arrow)

Case report

A 67-year-old man with a 5-cm infrarenal AAA underwent successful endoluminal tube graft repair with the Endovascular Grafting System (Endovascular Technologies, Menlo Park, California, USA). A completion arteriogram confirmed satisfactory graft deployment and no evidence of perigraft leak.

Follow-up with colour duplex scanning and contrast-enhanced computed tomography before discharge, and at 6 weeks (*Fig. 1a*) and 6 months after operation confirmed complete exclusion of the aneurysm sac. However, at 1 year follow-up, a distal perigraft leak was demonstrated (*Fig. 1b*). Intra-arterial digital subtraction angiography confirmed a posterior leak at the distal attachment site with antegrade perfusion of a lumbar artery (*Fig. 2*). In view of the patient's relatively young age, a decision was made to remove the endograft at open surgery.

At laparotomy the aneurysm was pulsatile and dilatation of the aortic bifurcation and the left common iliac artery was noted. Partial thrombosis of the aneurysm sac and a distal leak were confirmed after aortic clamping. The endoluminal graft was removed and the aneurysm replaced with an aortobi-iliac graft.

Discussion

Most of the early failures reported following endoluminal aneurysm repair have related to persistent proximal or distal perigraft leaks, leading to continued aneurysm expansion and even aneurysm rupture[2,4]. Of greater concern is the dilatation of the distal neck observed in this patient and also noted by Parodi in a few patients on long-term follow-up. This finding suggests that the biochemical changes within the aneurysm wall[5] may not be reversed by endoluminal grafting. If this is confirmed by others, the durability of endovascular aneurysm repair must be questioned. Continued aneurysm expansion may necessitate restriction of endovascular procedures to elderly patients and may also mandate the use of bifurcated, in preference to tube, grafts.

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British Journal of Surgery 1996, **83**, 543–546

Surgical workshop

Loop end colostomy: a new technique

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Permanent end colostomies are occasionally complicated by terminal gangrene, paracolostomy hernia, stricture formation, retraction or prolapse$^{1-3}$. A new technique of permanent end colostomy, 'loop end colostomy' which can minimize these complications, is presented.

Surgical technique

The distal end of the colon is closed with a linear stapler or handsewn in two layers according to the preference of the surgeon. A hole, through which the loop end colostomy will be constructed, is created in the abdominal wall by established methods. Once the distal colon has been thoroughly mobilized with preservation of its blood supply, the colon is pulled down until its lateral wall lies in close proximity to the hole in the abdominal wall, special care being taken to approximate the anterior taenia to the hole (*Fig. 1*). The lateral wall of the colon is then delivered through the hole and two stay sutures are placed in the anterior taenia from outside the abdomen. Subsequently, with seromuscular bites, the anterior taenia is sutured to the fascia transversalis for a length of about 5–7 cm intra-abdominally and the colonic serosa is sutured to the external oblique fascia extra-abdominally. The abdomen is closed after the lateral wall of the distal colonic end has been fixed to the fascia transversalis. The protruding lateral colonic wall is opened through the anterior taenia and the colon is sutured to the skin with interrupted 3/0 polyglactin whole-layer sutures.

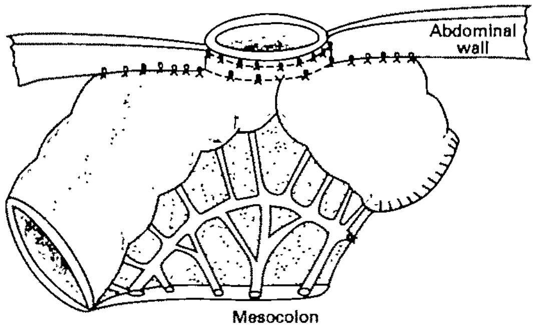

Fig. 1 Side view of a completed loop end colostomy

Discussion

The technique described here differs from other end colostomy techniques as it is a lateral colostomy procedure similar to a loop colostomy. With this technique, traction on the mesocolon is less and the probability of torsion of the colonic vascular pedicle is almost nil; the blood supply of the stoma and distal colonic end is well preserved, minimizing the risk of terminal gangrene.

Paracolostomy hernia is also avoided owing to the plugging effect of the sutured intra-abdominal portion of the distal colon. Prolapse is also less likely to occur with this technique because of the deviation of the axis of the bowel in comparison to that in conventional end colostomy. Furthermore, the distal end of the colon, once sutured to the lateral abdominal wall, cannot prolapse. Others[1,4,5] reported success with the use of synthetic mesh in preventing paracolostomy hernia and prolapse, but the present technique obviates the need for extra reinforcement.

Stricture formation at the stoma is known to occur more frequently in end colostomies than in other types. This technique, which involves a loop colostomy type of reconstruction, also minimizes the risk of stricture formation.

To date, this technique has been used in 53 patients with excellent results and no complications after a mean follow-up of 60 months (*Table 1*). All of these loop end colostomies were permanent. Use of this method is not advocated as a temporary means of faecal diversion because closure of a loop end colostomy would require further resection of the colonic proximal end which may result in traction at the anastomosis. Furthermore, during emergency operations in patients with inflammatory or diverticular disease, this technique may even be harmful since a potentially diseased colonic wall and/or intra-abdominal infection may compromise the healing of the intra-abdominal proximal colonic suture line. It should also be noted that the loop end colostomy is technically feasible only in patients in whom the thickness of the abdominal wall does not exceed the diameter of the colon pulled through; the afferent and efferent colonic segments will inevitably angulate acutely if pulled through an obese abdominal wall and the traction on the mesocolon will be similar to that in conventional end colostomy.

In conclusion, it is suggested that the loop end colostomy technique is the procedure of choice when a permanent terminal colostomy is required.

Table 1 Indications for loop end colostomy in 53 patients

Indication	No. of patients	Type of operation
Carcinoma of the rectum	47	Miles' operation
	3	Pelvic exenteration
Anal canal carcinoma	3	Miles' operation

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Paper accepted 5 September 1995

British Journal of Surgery 1996, 83, 812–815

An evaluation of the POSSUM surgical scoring system

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POSSUM (Physiological and Operative Severity Score for the enUmeration of Morbidity and mortality) has been studied as a possible surgical audit system for a 9-month interval using a sample of 28 per cent of the general surgical workload. Mortality or survival was analysed as an endpoint. In this sample the published POSSUM predictor equation for mortality overpredicted deaths by a factor of more than two. The bulk of the overprediction occurred in the group at lowest risk (predicted mortality 10 per cent or less), in which death was overpredicted by a factor of six. This is the most important group for audit purposes since it contains the majority of surgical patients and is composed of fit patients undergoing minor surgery. The published predictor equation for mortality returns a minimum predicted mortality of 1·08 per cent, clearly far higher than that expected for a fit patient having minor surgery. Logistic regression was done on a set of 1485 surgical episodes to generate a local predictor equation for mortality. This process gave a predictor equation that fitted well with the observed mortality rate and gave a minimum predicted risk of mortality of 0·20 per cent. The previously published POSSUM predictor equation for mortality performed badly when tested using a standard test of goodness of fit for logistic regression and must be modified.

Audit has become an essential part of routine surgical practice. Evidence of this is found in the advice document from the Royal College of Surgeons[1], the increasing number of papers on surgical audit in surgical journals and the frequent coverage of surgical audits, such as CEPOD (Confidential Enquiry into Perioperative Deaths), in the national media.

Data collection methods from different hospitals and surgical teams have not been standardized in the UK and meaningful comparisons between individuals, teams or hospitals are impossible. Simple collection of numbers alone is not sufficient to reflect treatment quality as, to compare morbidity and mortality data directly, the original populations must be identical. Surgeons treating a predominantly young population would be expected to achieve lower morbidity and mortality rates than others serving areas with an elderly population.

POSSUM (Physiological and Operative Severity Score for the enUmeration of Morbidity and mortality) has been proposed as a method for standardizing patient data so that direct comparisons of patient outcomes can be made in spite of differing patterns of referral and population[2]. This is done by allocating a score to 12 physiological variables measured on admission and then allocating a second score to the severity of the operative procedure that the patient undergoes. These scores are then inserted into two formulae that have been described previously[2,3], and risks of both morbidity and mortality can be predicted for the workload of each surgical team. The actual morbidity and mortality rates reported by a surgical team can then be compared with these predictions and individual patients who are either surgical successes or failures can be identified easily for close inspection at audit meetings.

Copeland *et al.*[2] originally assessed 48 physiological factors and 14 operative and postoperative factors. Using multivariate analysis these were reduced to 12 physiological and six operative factors (which were included to compensate for dependencies on surgical procedure that remained when physiological factors alone were used). These are summarized in *Table 1*. POSSUM does not take into account factors such as differences between surgeons, anaesthetists and operating time which might be expected to have considerable influence on outcome. These differences in surgical care, and hence perhaps outcome, are intended to be highlighted by POSSUM. The diagnosis also is not included; however, this is subsumed in the physiological state of the patient and in the operative findings, particularly in respect of malignancy. Copeland *et al.*[2] state that all hospitals in the UK have the ability to collect the complete POSSUM data set.

Table 1 POSSUM: physiological and operative parameters

Physiological parameters	Operative parameters
Age	Operative severity
Cardiac history	Multiple procedures
Respiratory history	Total blood loss
Blood pressure	Peritoneal soiling
Pulse rate	Presence of malignancy
Glasgow Coma Score	Mode of surgery
Haemoglobin	
White cell count	
Urea*	
Na^{+}*	
K^{+}*	
Electrocardiogram	

*From venous blood sampling

POSSUM has been compared favourably with the APACHE (Acute Physiology and Chronic Health Evaluation) II scoring system, which only takes physiological scoring into account and ignores the severity of operation[4]. The APACHE II scoring system is used mainly for scoring very sick patients and so the data required are more time-consuming to collect (e.g. blood gases). The majority of surgical patients are fit and having minor operations. A useful scoring system would be one that required only easily obtainable physiological variables that were appropriate to collect in all patients.

POSSUM appeared to fulfil this latter requirement and so it was decided to trial the POSSUM scoring system for

Paper accepted 14 September 1995

surgical audit in Portsmouth Hospitals (comprising two district general hospitals, Queen Alexandra and St Mary's). This initial trial was limited to testing the POSSUM equation for mortality, because of the extra difficulties involved in defining morbidity and in collecting data on complications, and the additional media interest in mortality data[5].

Patients and methods

Junior medical staff who saw patients on admission were required to document the physiological variables required by POSSUM. In an attempt to reduce extra work by junior doctors to a minimum, a printed multi-part structured history, examination, investigation, operation and discharge/outcome sheets were designed. Ward clerks were responsible for removing the copy sheet of each page from the notes and returning them to a central collection point. The structured sheets had each of the required variables outlined in a printed box and the data were easily transposed into a computer database by a clerk without the need to interpret any notes.

Day-cases and paediatric patients were excluded because they were treated in separate units outside the general surgical area. In addition, for consistency, the few planned day-case admissions to the general surgical unit were also excluded. Death in hospital was used as the endpoint since this was more feasible logistically than death within 30 days, especially given the increasing tendency to reduce outpatient follow-up appointments. Further, it is in-hospital mortality that is collected by the Hospital Information System (HIS) and it was intended to compare mortality figures of the present study with those on the HIS.

During the 9 months of the trial, some 1485 complete POSSUM data sets were obtained. This sample is slightly larger than that reported by Copeland *et al.*[2] and represented 28 per cent of patients having inpatient surgery during the trial.

Statistical analysis

The data were analysed using the BMDP statistical package (Los Angeles, California, USA)[6] on a mainframe computer. Frequency tables were compared by means of χ^2 tests, using the methods described by Hosmer and Lemeshow[7-10] as appropriate.

Results

Sample adequacy

It was necessary to show that the sample was representative of the general surgical workload. The distribution of length of stay of patients in the sample group was compared with that in the total general surgical workload taken from the HIS (*Fig. 1*). Length of stay is a good indicator of workload in that it is broadly indicative of both the severity of the operation performed and the physiological state of the patient. By its definition, length of stay allows for patients who died since they are considered to be discharged dead. The sample appeared to be representative of the general surgical workload of the hospital during the study interval as shown by the similar pattern of length of stay (*Fig. 1*). The proportion of postoperative deaths in the sample was similar to that in the total general surgical inpatient workload contained in the HIS (*Table 2*).

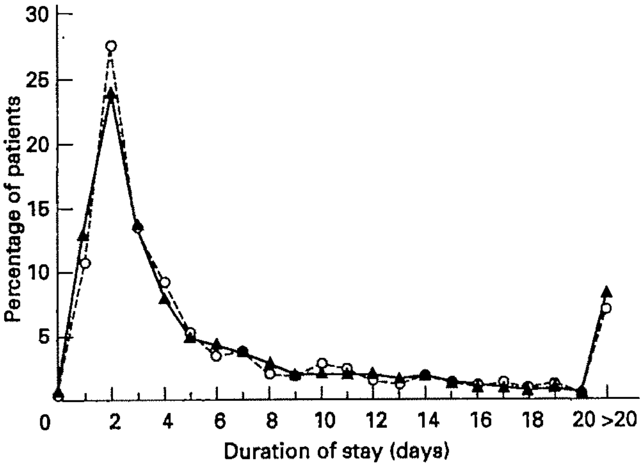

Fig. 1 Distribution of patients with duration of stay. Day cases are excluded. ▲, Hospital Information System ($n = 5250$); O, POSSUM trial ($n = 1485$)

Table 2 Comparison of the number of reported deaths from the study group and the Hospital Information System

	Operations	Reported deaths
POSSUM trial	1485	37 (2·49)
HIS	5250	126 (2·40)

Values in parentheses are percentages. Day-cases were excluded. $\chi^2 = 0{\cdot}074$, 1 d.f., $P = 0{\cdot}07854$ (χ^2 test, POSSUM trial *versus* Hospital Information System (HIS))

Table 3 Comparison of reported deaths and predicted deaths using Copeland predictor equation

Risk of death (%)	No. of operations	Mean risk (%)	Predicted deaths	Reported deaths
>0 to ≤4	1010	1·97	20	0
>4 to ≤10	278	6·10	17	6
>10 to ≤25	114	15·27	17	13
>25 to ≤60	71	37·74	27	12
>60 to ≤100	12	72·25	9	6
>0 to ≤100	1485	6·04	90	37

Analysis of deaths

The mortality predictor equation published by Copeland *et al.*[2] was applied, in which R is the predicted risk of mortality:

$$\ln[R/(1-R)] = -7{\cdot}04 + (0{\cdot}13 \times \text{physiological score}) + (0{\cdot}16 \times \text{operative severity score}).$$

However, a significant lack of fit was obtained with the sample data ($\chi^2 = 31{\cdot}53$, 1 d.f., $P < 0{\cdot}0001$). (The null hypothesis was that the equation would be an adequate fit; it follows that large χ^2 and correspondingly small P values are indicative of lack of fit.) The results summarized in *Table 3* show that the equation significantly overpredicted the total number of deaths, performing worst in low-risk patients.

Given this poor fit, logistic regression was done on the data using the BMDP package[6] to obtain a 'Portsmouth' predictor equation for mortality:

$$\ln[R/(1-R)] = -9{\cdot}37 + (0{\cdot}19 \times \text{physiological score}) + (0{\cdot}15 \times \text{operative severity score})$$

Table 4 Comparison of reported deaths and predicted deaths using Portsmouth predictor equation

Risk of death (%)	No. of operations	Mean risk (%)	Predicted deaths	Reported deaths
>0 to ≤4	1309	0·81	11	9
>4 to ≤10	96	6·07	6	9
>10 to ≤25	52	16·33	8	11
>25 to ≤60	21	34·87	7	5
>60 to ≤100	7	68·72	5	3
>0 to ≤100	1485	2·49	37	37

where R is the predicted risk of mortality. This equation was found to provide an adequate fit to the data ($\chi^2 = 5{\cdot}84$, 3 d.f., $P = 0{\cdot}1197$) (*Table 4*).

Discussion

POSSUM has been proposed as an accurate scoring system for auditing the outcome of patients who undergo surgery. It has the advantage of being simple and includes variables that are easy to collect. It takes into account both the admission physiology of the patient and the severity of the operation performed in predicting the rates of morbidity and mortality. POSSUM was evaluated in two district general hospitals over a 9-month interval in a trial including 1485 complete data sets. It was disappointing that the equation of Copeland *et al.*[2] performed so badly in predicting death in this data set and therefore the method of analysis was investigated in detail.

No details have been reported of how to apply the POSSUM system. Logistic regression was used to obtain the predictor equations and the equations themselves have been given, but there is no published method of testing the goodness of fit of the POSSUM predictor equation for mortality (or indeed morbidity) with the data set it is applied to. A suitable methodology has been described by Hosmer and Lemeshow[7–10] and this was used to test the result of applying both Copeland's predictor equation for mortality and the Portsmouth predictor equation obtained from logistic regression to the present data set.

The original equation[2] performed poorly in predicting the number of deaths. Overall, it overpredicted the number of deaths by more than a factor of two (90 *versus* 37). For patients with a predicted risk of death of 10 per cent or less it overpredicted the number of deaths by a factor of six (37 *versus* six); this represented the largest group of patients and arguably the most important since it included fit patients undergoing minor procedures. A successful comparative audit system must be effective in each region, and in all patient groups.

The lowest possible scores that POSSUM allows for physiology and operative severity are 12 and six respectively. Using Copeland's equation this will lead to the smallest risk of death being 1·08 per cent[11] for any patient no matter how fit or how minor the surgery. This is in conflict with previously published audits which suggest that the mortality rates of such patients, undergoing minor procedures, approach 0 per cent[12,13].

Using the Portsmouth equation and inserting the minimum POSSUM physiological and operative severity scores, a minimum predicted risk of mortality of 0·20 per cent was obtained. While this gives a good fit to the data set, the minimum risk of mortality of two per 1000 is probably still too high. This is a consequence of the method – it finds the best fit to the data set it is given and in doing so may well give an artefactually high minimum risk – logistic regression is constrained from giving risks below zero. In the practical application of a predictor equation from logistic regression it may be necessary to accept this artefact of the analysis and accommodate for it by setting the risk of death equal to zero when the physiological and operative scores are below predetermined cut-off levels. That is, statistical methods should not be applied blindly; practical experience should be used to modify the model.

The purpose of POSSUM is to remove differences between patient populations, and the inability of Copeland's equation to fit the present data set is hard to explain. Copeland *et al.*[2] excluded from their sample all patients for whom there was no 6-week outpatient review. It was not explicitly stated that a 30-day mortality rate was used. For this study death in hospital was used for pragmatic, logistical reasons and this must account for some of the differences observed. However, it is inconceivable that this could account for the 'missing' 20 deaths in the very low-risk group (*Table 3*).

A further possibility is that the POSSUM operative and physiological variables and/or the way in which they are scored are simply incapable of predicting death or are insufficient to do so. The fact that a predictor equation which fitted the present data well was obtained is strong evidence that the POSSUM variables can be used to predict mortality.

The Portsmouth predictor equation presented here is not the definitive equation for prediction of postoperative death in general surgery as these are the results of an initial trial. Geographical comparison of the use of POSSUM would be welcome, and as the database grows it is planned to test the adequacy of POSSUM when applied to individual surgeons. The application of a predictor equation that overpredicts mortality may lead to complacency by making mediocre or poor results appear good. It is therefore essential that any predictor equation is tested periodically for goodness of fit with the data to which it is being applied.

POSSUM is a powerful tool both for audit and research, but it should not be applied without care.

Acknowledgements

The authors thank the Medical Audit Committee of Portsmouth Hospitals NHS Trust for funding this trial, Dr Jane Dawson, Medical Audit Facilitator, for her enthusiasm and support, and Mrs Anne Walker, the hard pressed data entry clerk.

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British Journal of Surgery 1996, 83, 816–819

Diagnostic role of cytology in screen-detected breast cancer

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Fine-needle aspiration cytology (FNAC) of the breast was performed in 491 patients over a 3-year period. Some 365 examinations (74·3 per cent) were performed by palpation and the remaining 126 (25·7 per cent) by stereotaxis. Ninety-six patients were excluded because of inadequate follow-up. Using a standard method of reporting the results 247 smears were classified as C1 and C2, but based on clinical and radiological criteria excision biopsy was recommended and performed in 122 patients with these lesions. Twenty-two per cent of C2 lesions were found to be malignant after histological examination. Forty-two patients with C3 or C4 cytology were advised to have excision biopsy and 41 had surgery. In all but one case the lesion was found to be malignant histologically. Definitive surgery was performed on 106 patients with C5 cytology and the diagnosis of malignancy was confirmed histologically in 105 of them. FNAC is a useful diagnostic tool in breast screening but in view of the number of false-negative results, cytology alone is unreliable and, therefore, full triple assessment is recommended.

Fine-needle aspiration cytology (FNAC) is a valuable diagnostic tool in the symptomatic breast clinic[1,2]. It helps not only in the diagnosis of breast cancer but also in the planning of definitive treatment. FNAC has been shown to increase the diagnostic accuracy of mammography and clinical examination to 99 per cent[3]. FNAC has recently been introduced in breast screening units[4,5] and guidelines in taking and interpreting cytology smears have been produced and are included in the National Health Service Breast Screening Programme (NHSBSP) publication no. 22[6]. Radiological and clinical assessment achieve satisfactory benign:malignant ratios, but the introduction of FNAC will hopefully reduce the number of unnecessary biopsies of benign breast lesions even further. It has been reported that the benign:malignant ratio can be lowered to 1 : 7[7] and, in the *Quality Assurance Guidelines for Radiologists*[8], it is suggested that the number of benign biopsies, when FNAC is available, should be less than 20 per 10 000 women screened compared with less than 40 per 10 000 without FNAC. As many of the screen-detected lesions are impalpable, FNAC is performed after stereotactic localization[9–12].

The aim of this study was to evaluate the role of FNAC in the diagnosis of screen-detected palpable and impalpable breast lesions.

Patients and methods

The case records of 491 consecutive patients who underwent FNAC from January 1990 to December 1992 were studied. All the records were available and complete. Before FNAC, all patients had mammography and clinical examination, and some also underwent ultrasonography.

Aspiration of palpable lesions was performed with a 21-G needle attached to a 20-ml syringe, negative pressure being applied with a metal syringe holder (Cameco, Sweden). For impalpable lesions FNAC was performed under local skin anaesthesia by a radiologist, after stereotactic localization as described previously[6]. Local anaesthetic was not injected deep to the dermis to avoid contamination of the aspirate. The aspirated sample was processed immediately by a cytopathology technician. The material was ejected on to slides, spread thinly and immediately fixed, either by air-drying or by wet-fixing in ethanol. Rapid staining of air-dried slides was done by the M + D Diff-Quik technique (Merz + Dade, Düdingen, Switzerland) to enable immediate comment regarding the cellularity of the specimen. Later, in the laboratory, all slides were stained by May–Gruenwald–Giemsa and Papanicolaou methods as appropriate, and the needle rinse fluid was prepared by membrane filtration concentration (Millipore, Watford, UK). The smears were assessed by a consultant cytopathologist and the following standard method[6] of reporting the results was used: C1, inadequate specimen; C2, benign; C3, atypia probably benign; C4, suspicious of malignancy; C5, malignant.

After the FNAC result was made available, the further management of each patient was decided jointly by a surgeon and a radiologist. Lesions with a C1 or C2 classification were excised only when there were clinical and/or radiological features to suggest possible malignancy. Excision biopsy was recommended and performed in all patients with C3 or C4 cytology, apart from one patient with a C3 result who refused surgery. All lesions with C5 cytology were widely excised. In the few cases where mastectomy was deemed necessary because of the size or position of the cancer, the diagnosis of malignancy was confirmed before operation by Tru-Cut biopsy (Travenol Laboratories; Deerfield, Illinois, USA). Patients not having excision biopsy were followed up 3 months to 3 years after the initial assessment.

Results

Of the 491 FNAC examinations, 186 were performed in 1990, 149 in 1991 and 156 in 1992. The number of

Table 1 Breakdown of fine-needle aspiration cytology results by category and method of localization

	Cytological diagnosis					
	C1	C2	C3	C4	C5	Total
Palpation	34	205	5	30	91	365 (74·3)
Stereotaxis	32	72	0	7	15	126 (25·7)
Total	66 (13·4)	277 (56·4)*	5 (1·0)	37 (7·5)	106 (21·6)	491 (100)

Values in parentheses are percentages. *Ninety-six were excluded from further analysis because of inadequate follow-up

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Presented to the Joint Meeting of the European Society of Surgical Oncology, British Association of Surgical Oncology and Chirurgische Arbeitsgemeinschaft Onkologie der Deutschen Gesellschaft für Chirurgie in Heidelberg, Germany, June 1994 and published in abstract form as *Eur J Surg Oncol* 1994; 20: 254.
Paper accepted 5 September 1995

Table 2 Histological diagnosis of lesions with C1 cytology

	Palpation			Stereotaxis			Total		
	Total	Benign	Malignant	Total	Benign	Malignant	Total	Benign	Malignant
Biopsy	25	2 (8)	23 (92)	15	5 (33)	10 (67)	40	7 (18)	33 (82)
No biopsy*	9	8 (89)	1 (11)	17	15 (88)	2 (12)	26	23 (88)	3 (12)
Total	34	10 (29)	24 (71)	32	20 (62)	12 (38)	66	30 (45)	36 (55)

Values in parentheses are percentages. *It was assumed that lesions not excised after the initial assessment and which at follow-up were found to be clinically and radiologically unchanged were benign

Table 3 Histological diagnosis of lesions with C2 cytology

	Palpation			Stereotaxis			Total		
	Total	Benign	Malignant	Total	Benign	Malignant	Total	Benign	Malignant
Biopsy	59	30 (51)	29 (49)	23	15 (65)	8 (35)	82	45 (55)	37 (45)
No biopsy*	23	22 (96)	1 (4)	76	74 (97)	2 (3)	99	96 (97)	3 (3)
Total	82	52 (63)	30 (37)	99	89 (90)	10 (10)	181	141 (78)	40 (22)

Values in parentheses are percentages. *It was assumed that lesions not excised after the initial assessment and which at follow-up were found to be clinically and radiologically unchanged were benign

stereotactic procedures increased from 36 (19·3 per cent) in 1990 to 63 (40·4 per cent) in 1992. *Table 1* shows a breakdown of all FNAC results by category and method of localization. Specimens from only 66 patients (13·4 per cent) were inadequate. Of these patients, 40 underwent excision biopsy and 33 lesions were found to be malignant histologically. Of the 26 who did not undergo excision, only three were later found to have malignancy (*Table 2*). Overall, 55 per cent of C1 lesions were found to be malignant, but further analysis according to method of localization showed that 24 of 34 palpable C1 lesions were malignant compared with only 12 of 32 localized stereotactically.

More than half of the lesions screened by FNAC (56·4 per cent) fell into the C2 category. Ninety-six patients in this category were excluded from further analysis because of inadequate follow-up. As shown in *Table 3*, 45 per cent of patients undergoing excision biopsy of a C2 lesion were found to have malignancy compared with only 3 per cent of those who were followed up. As with C1 lesions, further analysis of C2 lesions according to method of localization showed some clear differences between palpable and impalpable lesions: (a) about half of the palpable C2 lesions biopsied were malignant compared with only about one-third of the impalpable ones; and (b) the percentage of palpable and impalpable C2 lesions that were malignant histologically was 37 and 10 per cent respectively. Overall, 22 per cent of the C2 lesions were malignant histologically and of these only 32·5 per cent were invasive ductal carcinomas (*Table 4*). The rest were mostly *in situ* ductal, invasive lobular and tubular or mixed cancers, all of which have been associated with false-negative cytological diagnoses[6]. Only five FNAC specimens (1 per cent of the total) were classified as C3 and four of the lesions were malignant. The fifth patient refused surgery and at follow-up 1 year later the lesion remained unchanged.

Table 4 Histological type of malignant lesions with C2 cytology

Type of carcinoma	*n*
Invasive ductal	13 (32)
In situ ductal	14 (35)
Mixed invasive and *in situ* ductal	7 (18)
Invasive lobular	4 (10)
Invasive tubular	2 (5)

Values in parentheses are percentages

Table 5 Histological diagnosis of lesions with C4 cytology

	Total	Benign	Malignant
Palpation	30	1 (3)	29 (97)
Stereotaxis	7	0 (0)	7 (100)
Total	37	1 (3)	36 (97)

Values in parentheses are percentages

Table 6 Histological diagnosis of lesions with C5 cytology

	Total	Benign	Malignant
Palpation	91	1 (1)	90 (99)
Stereotaxis	15	0 (0)	15 (100)
Total	106	1 (0·9)	105 (99·1)

Values in parentheses are percentages

Of 37 lesions with a C4 result, 36 proved to be malignant histologically (*Table 5*). The single benign lesion was an area of fibrocystic disease. Only one (0·9 per cent) of 106 lesions with C5 cytology was benign histologically (*Table 6*); its microscopic appearance was consistent with fibromatosis, which is a rare but recorded pitfall in FNAC of breast lesions[13] that can be mistaken for carcinoma clinically and radiologically.

In this study, the complete sensitivity of FNAC, defined in NHSBSP publication no. 22[6] as the number of

Table 7 Diagnostic accuracy of fine-needle aspiration cytology and triple assessment

FNAC	
Complete sensitivity	65·6
Full specificity	81·0
Positive predictive value of C5 result	99·1
Positive predictive value of C4 result	97
False-negative rate	18
False-positive rate	0·4
Inadequate rate	13·4
Triple assessment	
Sensitivity	97·3
Specificity	94·2
False-negative rate	2·7

Values are percentages. Inadequate samples were included in these calculations. For definitions and methods of calculation see reference 6. FNAC, fine-needle aspiration cytology

carcinomas that are not definitely negative or inadequate on FNAC expressed as a percentage of the total number of carcinomas, was 65·6 per cent and the specificity, defined as the proportion of benign lesions that are correctly diagnosed, 81·0 per cent. The positive predictive value of a C5 result, defined as the number of correctly identified cancers expressed as a percentage of the total number of C5 results, was 99·1 per cent and the sensitivity of triple assessment, i.e. combining cytology with clinical and radiological findings, was 97·3 per cent. These and other parameters relating to the accuracy of FNAC are shown in *Table 7*.

Discussion

FNAC is a simple and inexpensive tool that can be used in the management of screen-detected breast lesions. It is well tolerated by patients and can be used for impalpable masses and areas of microcalcification by using stereotactic localization. FNAC can reduce the number of operations performed by: (a) confirming the malignant nature of a breast lesion and therefore allowing the planning of definitive surgery and (b) identifying benign lesions that do not require open biopsy. In this series, FNAC enabled a firm preoperative diagnosis of malignancy to be made in 105 women (47·5 per cent of all patients with breast cancer). The number of false-positive results was very small (0·4 per cent). Definitive surgery was carried out on the basis of C5 cytology and in the majority of patients consisted of wide local excision of the abnormal area, with or without ipsilateral axillary node clearance. In the few patients in whom mastectomy was necessary, usually because of the size of the lesion, the diagnosis was confirmed before operation, in the case of palpable lumps by Tru-Cut biopsy and for impalpable lesions by an initial excision biopsy.

Patients with ductal carcinoma *in situ* (DCIS) and grade I invasive ductal carcinoma (IDC) measuring less than 1 cm in diameter do not routinely undergo axillary dissection. The decision whether to include axillary clearance in the first operation can be difficult because FNAC cannot reliably differentiate DCIS from IDC and cytological grading systems[14] are not in wide use. Moreover, although the size of a breast lesion can be measured radiologically, this does not always reflect the local extent of a carcinoma.

Sixty-six (13·4 per cent) of the aspirates in this series were inadequate. This compares favourably with the results of other studies[2,4,5,9], especially those which included only stereotactic FNAC of non-palpable lesions, and is well under the suggested maximum value of 25 per cent in NHSBSP no. 22[6]. Lofgren *et al.*[9] showed that FNAC of areas of microcalcification gave a higher percentage of inadequate samples than aspiration of non-palpable spiculated or circumscribed tumours.

False-negative results pose the biggest problem and make management decisions more difficult. Forty (22 per cent) of the present patients with a C2 result actually had a malignant lesion. There are at least three possible explanations for this figure. First, lesions detected by screening tend to be very small and, therefore, can be missed during aspiration. In this series stereotactic FNAC was more accurate than FNAC of palpable lumps, as shown by the number of false-negative results (10 per cent and 37 per cent respectively); stereotaxis should, therefore, be used more often, especially for lesions which are very small and difficult to localize by palpation. Second, many tumours contain both benign and malignant areas and it is possible that some of the aspirates were taken from a benign area. Third, interpretation of the slides can sometimes be difficult, especially in cases of DCIS and invasive cancers of a special type, e.g. tubular and lobular carcinomas, which can give a false-negative cytology result. In this series over 60 per cent of cancers with C2 cytology belonged either entirely or partly to these three categories of breast carcinoma. The decision whether to proceed to excision biopsy of a C2 lesion depends on its clinical and radiological features. Just under 50 per cent of the palpable C2 lesions biopsied were malignant histologically compared with only 35 per cent of the impalpable ones. This difference can easily be explained by the fact that clinical assessment is not possible for impalpable lesions and, therefore, the decision to operate is made purely on radiological grounds.

In this study, the positive predictive value of a C5 result was 99 per cent and that of a C4 result exceeded 97 per cent. The complete sensitivity of FNAC was only 65·6 per cent and the false-negative rate 18 per cent. However, the diagnostic accuracy was raised significantly by combining cytology with the results of clinical examination and imaging in the case of palpable lumps and with imaging for impalpable lesions. The sensitivity of this triple assessment was 97·3 per cent and the false-negative rate 2·7 per cent.

This study covers cytology aspirates examined in the first 3 years after this unit was set up. As with any new procedure, there is a learning curve and Warren[7] has shown that FNAC can become more effective in reducing the benign to malignant ratio after 5 years' experience. During this 3-year period the authors achieved a ratio of benign to malignant lesions excised of 1 : 3·98, which compared favourably with the national average of 1 :1·5[15].

These results suggest that FNAC plays an important role in the management of screen-detected breast lesions. It reduced the number of patients undergoing operation for benign breast disease and allowed the planning of definitive surgery for malignant breast lesions. However, in many cases axillary dissection can only be done as a separate procedure after the histological type and grade of the tumour has been established.

In view of the number of false-negative results cytology alone is unreliable and it should be used in breast screening as part of a full triple assessment by clinical examination, radiology and cytology in the case of palpable lesions, and double assessment by radiology and cytology for impalpable tumours. This study demonstrates that this approach achieves a high preoperative diagnostic accuracy.

Acknowledgements

The authors thank Drs H. Fadl and S. Gilani for performing some of the stereotactic fine-needle aspirations and are grateful to the Buckle Family Trust for funding C.Y.

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British Journal of Surgery 1996, 83, 820–822

Periductal mastitis and duct ectasia: different conditions with different aetiologies

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A prospective study of 14 225 patients has been undertaken to determine the inter-relationship between periductal mastitis and duct ectasia and to establish whether there is an association between smoking and either of these two conditions. Periductal mastitis affected women at a younger age than did duct ectasia. Of 139 patients with the clinical syndrome of periductal mastitis, 97 (70 per cent) had a past history of previous periductal mastitis, compared with only one (1 per cent) of 186 patients with the clinical syndrome of duct ectasia ($P < 0.0001$). There was a significant excess of smokers in patients with clinically (124 (89 per cent) of 139) and pathologically (71 (91 per cent) of 78) diagnosed periductal mastitis compared with age-matched controls (both $P < 0.001$), but there was no such excess in those with clinically (52 (28 per cent) of 186) or pathologically (15 (23 per cent) of 64) diagnosed duct ectasia. These data suggest that periductal mastitis and duct ectasia are separate conditions which affect different age groups, have different aetiologies, and should now be considered as separate entities.

Previous studies have demonstrated that, if periductal mastitis and duct ectasia are part of the same disease process, periductal mastitis precedes duct ectasia[1]. Recent evidence indicates that smoking is a major factor in the aetiology of periductal mastitis and its complications[2,3]. If these two conditions are related, patients with duct ectasia would be expected to have a past history of periductal mastitis and the two conditions should have a similar relationship with smoking. The present study investigated the inter-relationship between periductal mastitis and duct ectasia and the association of these two conditions with smoking.

Patients and methods

A prospective study was performed on 14 225 patients presenting to the Edinburgh Breast Unit over a 4-year period, from January 1989 to December 1992. For all patients a computerized pro forma was completed and data collected included details of any previous breast disease including the nature of the disease, whether they were current smokers, and clinical and subsequent pathological diagnosis.

Patients were considered to have periductal mastitis if they presented with a periareolar inflammatory mass, a non-lactational abscess or a mammary duct fistula. Patients were considered as having mammary duct ectasia if they had recently developed isolated slit-like nipple retraction with or without nipple crusting or spontaneous cheesy nipple discharge. Patients with other types of spontaneous discharge were not considered to have duct ectasia.

During the study period, 139 patients were classified as having clinical periductal mastitis: 68 had a periareolar inflammatory mass, 39 a non-lactational periareolar abscess and 32 a mammary duct fistula. There were 186 patients with clinically diagnosed duct ectasia.

Some 142 of the 325 patients with clinical periductal mastitis or duct ectasia underwent operation: 78 had a histological diagnosis of periductal mastitis (characterized by active periductal inflammation and the absence of or minimal duct dilatation[1]) and 64 were diagnosed as having duct ectasia (characterized by prominent duct dilatation and minimal or moderate periductal chronic inflammation[1]). All 78 patients who had histological evidence of periductal mastitis were from the group of 139 with clinical periductal mastitis; similarly, the 64 patients with pathologically diagnosed duct ectasia belonged to the group of 186 diagnosed clinically as having duct ectasia.

The numbers of patients with a history of previous benign disease and the numbers of current smokers in diagnostic groups were compared with those in groups of patients with the same age range who had attended the breast clinic but did not have either of these two conditions. Comparisons between the groups were performed with the χ^2 test. Differences in the age distribution of different conditions were assessed by the Wilcoxon rank sum test.

Results

Clinical periductal mastitis (periareolar inflammatory mass, a non-lactating abscess or a mammary duct fistula) affected a significantly younger age group than patients with duct ectasia ($P < 0.0001$). Although age-matched groups were identified on the basis of age range, these groups had similar median ages to patients with clinical periductal mastitis or duct ectasia (*Table 1*).

Previous breast disease

Of the total group of 14 225 patients, 4865 (34 per cent) had a history of previous benign breast disease. The incidence of previous breast disease increased as the age of patients increased. The groups of patients with periareolar inflammatory masses, non-lactational abscesses and mammary duct fistulas each had an excess of patients with a previous history of benign breast conditions when compared with age-matched control groups (all $P < 0.0001$). In contrast, each group of patients with clinically diagnosed duct ectasia were significantly less likely to have had previous breast disease than subjects in an age-matched control group ($P < 0.01$) (*Table 2*). When specifically examining previous episodes of clinical periductal mastitis, 97 patients (69 per cent) in the periductal mastitis group and one (1 per cent) with duct

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Paper accepted 20 September 1995

Table 1 Age distribution of patients with periductal mastitis and duct ectasia

	Patients		Age-matched group	
	n	Median (range) age (years)	*n*	Median age (years)
Periareolar inflammation	68	33 (19–48)	10 397	34
Non-lactational abscess	39	35 (23–46)	8 944	35
Mammary duct fistula	32	37 (26–48)	9 231	36
Duct ectasia	186	58 (42–85)	9 093	59

Table 2 History of previous benign breast disease in patients with periductal mastitis and duct ectasia

	Patients		Age-matched group	
	n	No. with previous breast disease	*n*	No. with previous breast disease
Periareolar inflammation	68	37 (54)*	10 397	4 044 (39)
Non-lactational abscess	39	28 (72)*	8 944	3 497 (39)
Mammary duct fistula	32	32 (100)*	9 321	3 887 (42)
Duct ectasia	186	52 (28)†	9 093	4 092 (45)

Values in parentheses are percentages. $^*P<0{\cdot}0001$, $^\dagger P<0{\cdot}01$ *versus* age-matched controls (χ^2 test)

Table 3 History of previous periareolar inflammation in patients with periductal mastitis and duct ectasia

	No. of patients	No. with previous periductal mastitis
Periareolar inflammation	68	37 (54)*
Non-lactational abscess	39	28 (72)*
Mammary duct fistula	32	32 (100)*
Duct ectasia	186	1 (1)

Values in parentheses are percentages. $^*P<0{\cdot}01$ *versus* duct ectasia group (χ^2 test) combining periareolar inflammation, non-lactational abscess and mammary duct fistula patients *versus* duct ectasia patients, $P<0{\cdot}0001$

ectasia had a history of this condition; the difference between groups was statistically significant ($P<0{\cdot}0001$) (*Table 3*).

Table 4 Smoking related to clinical diagnosis

	Patients		Age-matched group	
Clinical diagnosis	*n*	No. of smokers	*n*	No. of smokers
Periareolar inflammatory mass	68	60 (88)*	10 397	3 955 (38)
Non-lactational abscess	39	34 (87)*	8 944	3 441 (38)
Mammary duct fistula	32	30 (94)*	9 321	3 504 (38)
Duct ectasia	186	52 (28)	9 093	2 722 (30)

Values in parentheses are percentages. $^*P<0{\cdot}001$ *versus* age-matched controls (χ^2 test)

Table 5 Smoking related to pathological diagnosis

	Patients			Age-matched group	
Pathological diagnosis	*n*	Age range (years)	No. of smokers	*n*	No. of smokers
Periductal mastitis	78	21–46	71 (91)*	9202	3546 (39)
Duct ectasia	64	43–81	15 (23)	8461	2510 (30)

Values in parentheses are percentages. $^*P<0{\cdot}001$ *versus* age-matched controls and smokers with duct ectasia (χ^2 test)

Smoking history

Of the 14 225 patients, 4695 (33 per cent) were smokers. Smoking was related to age, with the highest percentage of smokers in women under the age of 40 years. When the number of smokers in patients with clinical periductal mastitis or its complications was compared with the number in age-matched groups, there was a significant excess of smokers in all three of the groups of patients with periductal mastitis (*Table 4*) (all $P<0{\cdot}001$). Patients with duct ectasia were no more likely to be smokers than subjects in an age-matched control group. An excess of smokers was also noted in patients with a pathological diagnosis of periductal mastitis ($P<0{\cdot}001$), but there was no excess of smokers in those with pathologically diagnosed duct ectasia (*Table 5*).

Discussion

The present and previous studies have shown that periductal mastitis affects a younger age group than duct ectasia[1]. If these two conditions are related, periductal mastitis would be expected to precede duct ectasia and thus patients with duct ectasia should commonly have a history of periductal mastitis. This study has demonstrated that, although patients presenting with signs and symptoms of periductal mastitis frequently have a history of previous periareolar inflammation, very few with duct ectasia have a past history of periductal mastitis. This suggests that the two conditions are probably unrelated, and is supported by studies on the aetiology of the two conditions. Anaerobic bacteria have been identified from the lesions of what is now considered to be periductal mastitis, but they have not been identified in lesions that are now classified as duct ectasia[4,5]. In the present study these two conditions have also been demonstrated to have different associations with smoking. Approximately 90 per cent of patients identified as having clinically or pathologically diagnosed periductal mastitis were current smokers compared with less than 30 per cent in those with duct ectasia. Smoking may damage the subareolar ducts either as a direct toxic effect or as an indirect effect on hormones or blood flow, and the lesions may then become infected with anaerobic bacteria[6].

Although it has been considered that periareolar inflammation seen in patients with periductal mastitis damages the supporting elastic lamina of the ducts, which then leads to duct ectasia[1,7], this is incompatible with the results of the present study; it is likely that duct ectasia, the frequency of which increases with age, is a simple aberration of the normal ageing process[8]. Periductal mastitis and duct ectasia appear to be separate clinical and pathological entities, which affect different age groups and have different aetiologies, and they should be considered as two separate conditions.

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British Journal of Surgery 1996, 83, 823–827

Parathyroidectomy in the West Midlands

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A retrospective audit was made of 101 patients undergoing parathyroidectomy, performed by 20 general surgeons in the West Midlands region during 1992. The mean number of cases per surgeon was five; nine surgeons performed fewer than three parathyroidectomies. Some 57 patients had primary hyperparathyroidism. Only seven were diagnosed by general practitioners and referral was invariably to a non-endocrine physician. Delay between diagnosis and surgical referral exceeded 2 years in 12 patients. Four patients (7 per cent) with primary hyperparathyroidism remained hypercalcaemic after first exploration; all were operated on by surgeons who performed fewer than four parathyroidectomies per year. Minor complications occurred in 32 per cent of patients. All 44 patients with renal hyperparathyroidism were treated in specialist units where diagnosis and treatment were expeditious; parathyroidectomy was successful in 41. Hyperparathyroidism should be managed in specialized units and by surgeons who perform parathyroidectomy frequently. A heightened awareness of primary hyperparathyroidism is required at primary care level.

Following the introduction of multichannel biochemical autoanalysers, primary hyperparathyroidism (HPT) has been diagnosed with increasing frequency[1–3] and is now recognized as a common disorder. Secondary HPT requiring parathyroidectomy has also become more common as the number of patients treated for renal failure has grown.

Parathyroidectomy has traditionally been performed by general surgeons. Parathyroid disase tends to present to a number of disciplines which individually may encounter the problem infrequently and it is not surprising that delays in diagnosis and treatment have been reported[4]. In the West Midlands region of England (population 5·2 million) several units, including the authors', perform parathyroidectomy. The objective of this study was to assess the quantity and quality of parathyroid surgery within the region and to identify means by which the management can be improved.

Patients and methods

The audit period was 1 January to 31 December 1992, allowing follow-up of between 22 and 36 months. Questionnaires were sent to all general surgeons and urologists in the region enquiring about their involvement in parathyroid surgery and seeking permission to include their patients in an audit. A retrospective review was then done using patients' notes obtained from units agreeing to participate. If records were not available, visits were made to the units and searches performed through other documentary sources such as theatre records and histopathology reports. In a few cases additional follow-up data were obtained from general practitioners.

Results

Some 104 general surgeons in the West Midlands were sent questionnaires; 99 replies were received. Thirty-four surgeons (33 per cent) reported that parathyroid surgery was included in their practice but only 20 (19 per cent), from 14 units, performed parathyroidectomy during 1992. All 20 agreed to be included and information obtained with their permission constitutes the database of this study. None of the region's urologists performed parathyroidectomy.

A total of 101 patients were identified who had undergone parathyroidectomy during 1992. Detailed information was available on 97 patients and limited details on four.

The mean number of parathyroidectomies performed per surgeon during 1992 was five (range 1–40). If the surgeon who performed 40 procedures was excluded, the mean number for the remainder was three per surgeon. Three surgeons performed two and six surgeons performed only one parathyroidectomy.

In 90 patients, operation notes indicated that parathyroidectomy had been performed by, or under the direct supervision of, a consultant surgeon. In two cases (one primary, one renal) the procedures were performed by higher surgical trainees without direct supervision. In nine patients operation notes were not available or were inadequate to identify the grade of the operating surgeon. Re-explorations for persistent or recurrent HPT were all performed by consultants.

Only two surgeons used methylene blue. All surgeons employed frozen section histology, the findings of which were confirmed by paraffin histology in 92 (98 per cent) of 94 documented cases.

Primary parathyroid disease

Fifty-seven patients (48 women, nine men; mean age 60 years) had parathyroidectomy for biochemically proven primary HPT. Fifty-three patients had first time explorations and four, unsuccessfully explored before 1992, underwent re-exploration.

In 34 patients (58 per cent) the diagnosis of primary HPT was made by a consultant physician. General practitioners made the diagnosis in only seven cases (12 per cent) despite having been the source of initial medical referral in all patients. Five patients (9 per cent) who presented with abdominal pain had the diagnosis made by general surgeons. Five patients, all with renal calculi, were

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Presented to the British Society of Endocrine Surgeons in Belfast, June 1994 and at Eurosurgery '94 in Berlin, October 1994, and published in abstract form as *Br J Surg* 1994; 81(Suppl.): 44.
Paper accepted 3 October 1995

identified by urologists. Information on six patients was not available.

A long delay often occurred between the diagnosis of hypercalcaemia and surgical referral. In 45 patients (79 per cent) this interval was less than 1 year but in 12 (21 per cent) a delay of more than 2 years up to a maximum of 19 years was experienced (*Table 1*). The mean time from surgical referral to operation was 4 months (range 2 weeks to 13 months).

Localization studies were performed before first exploration in 15 patients with primary HPT. Ten studies were initiated by physicians before referral to a surgeon and five by the operating surgeon. Eight patients had ultrasonography, four had subtraction isotope scans, two had both and one had ultrasonography and computed tomography of the neck. The small number of each investigation precludes any detailed comparison, but their overall accuracy was poor. The correct side and site of the adenoma was identified in only two of 15 patients. In the remainder localization was inaccurate; side only was correct in four patients and false-negative results were reported in the other nine.

Localization studies were performed on all five patients who had re-exploration for persistent primary HPT, at the request of the operating surgeon. Accurate localization (correct side and site) was achieved in three.

Fifty-three patients had first time exploration and in all cases this included bilateral neck dissection. Forty-one (77 per cent) patients had a single adenoma removed, but in 13 of these it was impossible to assess the exact nature of the procedure performed (i.e. side and site of adenoma, biopsy of normal glands) from the operation records. In five patients (9 per cent) two or more enlarged glands were removed. Histologically all demonstrated features of hyperplasia. In two patients two hyperplastic glands were resected and in three patients three hyperplastic glands were removed. In four patients (*Table 2*) none of the tissue removed at operation proved to be abnormal parathyroid when subjected to histological examination although in three of these patients normal parathyroid glands were included in the resected tissue. All four patients were operated on by surgeons who performed fewer than four parathyroidectomies during the study year. The operative findings in three patients were unknown.

Forty-nine of the 53 patients (92 per cent) who had first explorations became normocalcaemic. Only one of the four patients who remained hypercalcaemic has subsequently been re-explored.

Thirty-two patients reported an improvement in their overall feeling of well-being although none underwent objective testing. No details of symptoms were documented during the follow-up of 20 patients.

The outcome of re-exploration of four patients with persistent/recurrent HPT previously explored before the study are shown in *Table 3*.

Documented morbidity occurred in 18 of 57 patients (31 per cent) but was relatively minor (*Table 4*). There

Table 1 Patients with primary hyperparathyroidism who experienced delay before surgical referral

Patient no.	Sex	Age (years)	Symptoms	Serum Ca^{2+} (mmol/l)	Duration (years)	History
1	F	72	Abdominal pain, thirst	3·3	2	Initially treated medically
2	F	33	Incidental	2·7	3	Followed up only
3	M	73	Bone pain	2·9	3	Not referred. PTH only marginally raised
4	F	66	Depression	3·2	4	Followed up only
5	F	78	Bone pain, polyuria	2·8	5	Treated as Paget's disease
6	M	70	Bone pain, polyuria	2·8	5	Ca^{2+}-reducing diet
7	F	68	General malaise	3·5	7	Followed up only
8	F	71	General malaise	2·9	7	Not referred. 'Stable' hypercalcaemia and three negative localization studies
9	M	64	Renal calculi	2·9	12	Initially untreated, then fluid regimen
10	F	52	Asymptomatic	2·8	12	Followed up only. Referred for thyroid nodule
11	M	72	Bone pain	3·0	13	Initially discharged. Finally referred for thirst and polyuria
12	F	75	Renal calculi	3·2	19	Initially untreated. Re-presented with malaise

PTH, parathyroid hormone

Table 2 Presentation and outcome in patients with persistent primary hyperparathyroidism after first neck exploration

Age	Sex	Presenting symptoms	Preoperative Ca^{2+} (mmol/l)	Postoperative Ca^{2+} (mmol/l)	Outcome
60	F	Depression	2·7	2·7	Continuing psychiatric problems; refused re-exploration
68	F	Depression	2·7	2·7	Discharged from follow-up by junior surgical staff
59	F	Malaise, thirst, polyuria	3·4	3·6	Mediastinal mass on computed tomography. Intrathymic PTA removed via sternal split. Normocalcaemic
73	M	Bone pain, renal calculi	3·0	2·9	Asymptomatic. Declined re-exploration

PTA, parathyroid adenoma

Table 3 Patients who had re-exploration for persistent or recurrent primary hyperparathyroidism who had previous surgery before 1992

Age	Sex	No. of previous explorations	Parathyroids removed previously	Details of new presentation	Procedure	Outcome
72	F	2	Not known	Bone disease, renal calculi, Ca^{2+} = 3·34 mmol/l	Right and left upper PTAs removed	Normocalcaemia
51	F	1	Not known	Bone disease, renal calculi, Ca^{2+} = 2·8 mmol/l	Sternal split: mediastinal PTA removed	Normocalcaemia
61	F	1	Right and left, lower PTAs	Depression, Ca^{2+} = 3·3 mmol/l, normal PTH level measured twice	Tumour found in root of neck. Biopsy→ squamous carcinoma	Died on day 4 after operation from respiratory complications related to tumour
66	F	1	Four hyperplastic glands	Asymptomatic, normal calcium, raised PTH	Mediastinal exploration during elective aortic valve replacement	No PTAs found. Now asymptomatic with Ca^{2+} = 2·67 mmol/l

PTH, parathyroid hormone, PTA, parathyroid adenoma

Table 4 Complications of parathyroidectomy for primary hyperparathyroidism

Complication	No. of patients
Temporary hoarseness	3
Temporary hypocalcaemia requiring intravenous Ca^{2+} supplementation	9
Persistent wound pain	3
Discharging wound sinus	1
Keloid scar	1
Death	1

were no permanent recurrent laryngeal nerve (RLN) palsies. One postoperative death was caused by a non-parathyroid malignancy identified during a re-exploration procedure (*Table 3*).

Renal hyperparathyroidism

Forty-four patients (22 women, 22 men; mean age 43 years) had a neck exploration for secondary HPT. All had chronic renal failure or renal transplants. The procedures were performed in five hospitals, all with renal units, in which the patients had been under follow-up by a nephrologist who made the diagnosis in all cases. There was no delay in diagnosis or referral for surgery and all patients had parathyroidectomy within 6 months of developing symptoms.

Some 41 patients had first time explorations, of whom 30 had total parathyroidectomy with parathyroid autografting. Three patients had formal subtotal parathyroidectomy in which three and a half glands were removed. In four patients, only three glands were identified and removed and in two patients only two glands were removed. Details of the procedure performed in two patients were not available.

Secondary disease was controlled in 38 of the 41 patients undergoing first explorations but persisted in three.

Three patients had repeat parathyroid exploration for persistent secondary HPT having previously been explored before 1992. In all three patients secondary HPT was controlled.

There were no deaths in this group and no cases of RLN palsy. Postoperative hypocalcaemia delayed discharge from hospital in 20 patients (46 per cent). Hypocalcaemia was usually not symptomatic and was controlled by oral calcium and 1-α calcidol if below 2·0 mmol/l, but three patients required intravenous calcium for symptomatic hypocalcaemia.

Discussion

Only five surgeons failed to reply to the questionnaire; additional enquiries have indicated that they do not perform parathyroidectomy. It was surprising that as many as one-third of general surgeons include parathyroidectomy in their practice. However, many respondents performed fewer than five procedures per year. In the hands of experienced surgeons, parathyroidectomy is a highly successful operation with a cure rate for primary HPT of 90–95 per cent[5–8] but results are undoubtedly worse when it is performed by less experienced surgeons[9–11]. Indeed, in all four of the cases of primary HPT not cured by the first operation in this series, the surgeon involved had performed fewer parathyroidectomies per year than the mean. There is a case for concentrating parathyroid surgery in fewer specialized units: in this survey 11 of 104 general surgeons performed the bulk of the operations, suggesting that two parathyroid surgeons per million population would be required.

Consultants performed all but two of the parathyroidectomies in this series and trainees seeking specific instruction in parathyroid surgery would also benefit from the development of specialized parathyroid centres.

The clinical presentation of primary HPT has changed and this study is typical of contemporary series in which postmenopausal women predominate[12,13].

Routine screening of serum calcium has increased the incidence of asymptomatic primary HPT to 100 per 100 000 of the general population[2,14] whilst in women over the age of 60 years incidences from 180[2] to 1300 per 100 000[1,15] have been reported. However, the condition remains underdiagnosed: Swedish[3] and American[16] data suggest that only 10 per cent of patients with primary HPT are identified. In the present series the rate was 1·1 patients per 100 000 population, although a few other operations may have been performed in private hospitals.

Difficulties in diagnosing primary HPT begin in primary care. All patients in this series were initially seen by their general practitioner but the diagnosis was made in only 12 per cent of cases and most patients were referred either without the benefit of serum calcium estimation, or with the results poorly interpreted. Many patients suffered delays in treatment because the diagnosis was not made and specialist referral was ill directed.

In some patients, although the diagnosis was made promptly, there was often a period of further investigation or trial of medical treatment. Others were not referred for surgery because their hypercalcaemia was considered 'stable' or because localization studies failed to reveal parathyroid enlargement. In most patients there is neither clinical nor economic benefit in treating primary HPT medically[2] and the delays encountered appear to represent a reluctance to consider surgery, particularly for elderly patients with apparently minimal symptoms. However, the risks associated with modern parathyroid surgery are small and unless there are compelling medical contraindications, parathyroidectomy should be performed even in asymptomatic patients[14].

In the previously unexplored neck, preoperative localization studies do not improve the rate at which an experienced parathyroid surgeon locates adenomas[17], reduce operating time[10] or costs[18–20], or improve safety[17] and are unnecessary[21,22]. However, localization studies continue to be performed on a substantial number of patients[15], including a quarter of the patients in this series who had first explorations for primary HPT. These investigations were usually arranged by physicians before surgical referral, and contributed little to management.

The standard surgical treatment for primary HPT is excision of all adenomas after visualizing all four parathyroids and providing biopsy evidence that remaining glands are normal. However, since in approximately 90 per cent of individuals the underlying lesion is a solitary adenoma, unilateral exploration of the neck has become an attractive surgical option[23]. The procedures performed in this study all involved traditional bilateral cervical exploration although in many cases operation notes failed to document accurately which parathyroids had been removed and/or biopsied. This information is of great importance if re-exploration is necessary.

Few problems were encountered managing single adenomas but difficulties were experienced treating multiple gland hyperplasia (MGH). Fewer than four glands were resected in all patients with MGH despite the condition being recognized at operation. MGH is rare and individual experience limited, but subtotal parathyroidectomy has become the procedure of choice which may also include transcervical thymectomy in search of a fifth gland[24]. Patients with MGH in this series remain well but since the initial parathyroid resections were incomplete there remains a potential for recurrent HPT.

Ideally patients should be reviewed after parathyroidectomy until normocalcaemia has been documented. Although this usually requires only one clinic visit for patients with single adenomas, more than half the patients in this study were subjected to costly long-term follow-up. Patients should be reviewed by experienced clinicians since persistent hypercalcaemia passed undetected in one patient in this series who was discharged from follow-up by an inexperienced junior surgeon (*Table 2*).

Re-exploration for persistent or recurrent HPT is a difficult procedure associated with a reduced cure rate[25,26], an increased risk of RLN injury[27,28] and permanent hypocalcaemia[27,29]. Asymptomatic patients with mild to moderate persistent hypercalcaemia (serum calcium less than 2·9 mmol/l) probably fare better without further surgery. If reoperation is performed, an unequivocal diagnosis of primary HPT based on persistently raised serum calcium and parathyroid hormone (PTH) must be established and the risks discussed with the patient. One patient in this series, in whom no abnormal parathyroid tissue was found, was re-explored (and subsequently died from an unsuspected malignancy) despite two normal PTH measurements.

Following initial exploration the overall cure rate for primary disease in this series was 92 per cent, comparable to that of other reports[5–9,30]. The procedure was associated with low morbidity and mortality rates and the fear of surgical risks appears an insufficient reason to deny operation, even to elderly patients.

Secondary HPT requiring parathyroidectomy occurs in up to 30 per cent of patients receiving chronic dialysis[31] despite medical treatment with phosphate binders and 1-α calcidol. The incidence continues to increase and in this series secondary HPT was the indication for operation in 44 per cent of patients. All were under long-term review by a nephrologist and little delay in diagnosis and treatment occurred. Parathyroidectomies for secondary HPT were performed in units undertaking above average numbers of procedures. Total parathyroidectomy with immediate autografting was the preferred procedure although in six patients incomplete resection (three or fewer glands removed) was documented. Despite this, secondary HPT was controlled in 95 per cent of cases, a result comparable with other reported series[32–34]. Morbidity was low although hypocalcaemia was common after operation.

The results of parathyroidectomy in the West Midlands during 1992 compare favourably with those of other major series. However, significant problems, particularly affecting patients with primary HPT, have been uncovered. Poor rates of diagnosis occurred at primary care level. Hospital referral was often ill directed resulting in overinvestigation, trials of inappropriate medical treatment and unacceptable delay before operation. Furthermore, parathyroidectomy was too often performed by 'occasional' rather than specialist parathyroid surgeons.

Parathyroid disease is common and increasing numbers of parathyroidectomies are likely to be required in future. Increasing the awareness of primary HPT among general practitioners, particularly when assessing postmenopausal women with persistent neuro/psychiatric symptoms, would improve diagnosis and direct referral towards surgical treatment eliminating the delays associated with intermediate consultations. There may be considerable advantage if patients with HPT are managed in fewer, more specialized endocrine units by surgeons with a special interest in parathyroid surgery.

Acknowledgements

The authors thank the surgeons of the West Midlands who allowed their data to be included in this study, and their secretarial staff for assistance in collecting the data.

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British Journal of Surgery 1996, **83**, 828–829

Magnetic resonance imaging of thyroid swellings

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The preoperative diagnosis of some thyroid neoplasms remains difficult even with the routine use of fine-needle aspiration cytology. The potential of nuclear magnetic resonance imaging (MRI) to discriminate between different thyroid pathologies was explored prospectively and compared with the final pathology in a series of 37 patients. MRI yielded high-quality images of the thyroid swelling but did not provide additional information to differentiate benign from neoplastic lesions. MRI does not contribute to the routine management of thyroid swellings.

The detection and excision of neoplasms are primary objectives in the management of thyroid swellings. Clinical features including age, sex and physical characteristics of the swelling are useful indices for malignancy. However, it may be impossible to establish a diagnosis before surgery, particularly in follicular neoplasms, even with routine use of fine-needle aspiration cytology (FNAC)[1–3]. Magnetic resonance imaging (MRI) is a powerful imaging technique capable of demonstrating both anatomical and, possibly, pathological characteristics of a swelling[4]. The aim of this study was to compare MRI with the gross pathology and histology in patients having thyroid surgery.

Patients and methods

Thirty-seven consecutive patients who had thyroid surgery between October 1992 and April 1993 were studied. All patients had routine thyroid function tests, serology and FNAC. Chest radiography with thoracic views was performed when indicated. MRI was performed on the day before surgery.

A 1·0 T Siemens Impact scanner (Siemens, Erlangen, Germany) was used. Coronal and transverse, T1 and T2 weighted scans were obtained. Image-enhancing software was available which allowed the acquisition of images in 15–20 s. This reduced movement artefact and enhanced patient compliance. In addition, gating was employed in the glottic region to further reduce movement artefact. Following thyroidectomy the specimens were marked by the surgeon to permit accurate orientation by the pathologist. Sections were then cut which could be compared directly with the MRI scan sections. The specimens were photographed before histopathology blocks were taken. The scans, gross pathology and histopathology were compared retrospectively to determine whether there were any consistent features.

Results

Six men and 31 women entered the study. The definitive pathology is shown in *Table 1*. Image quality was satisfactory in all but five patients in whom detail was reduced by movement artefact. The T1 scan showed more detail whereas the T2 scan gave more contrast but less resolution. A typical T2 scan of a papillary cancer is shown in *Fig. 1* with the pathology in *Fig. 2*. Large cystic lesions gave a uniformly homogeneous appearance. The

Table 1 Definitive pathology of thyroid swellings

Non-neoplastic ($n = 22$)	
Colloid degeneration	14
Cyst	3
Colloid adenoma	5
Neoplastic ($n = 15$)	
Follicular adenoma	6
Follicular carcinoma	6
Papillary carcinoma	3

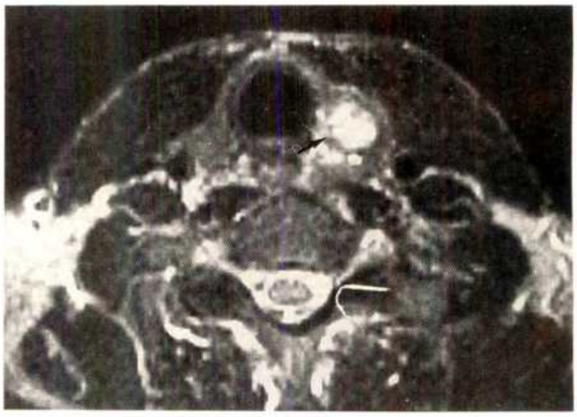

Fig. 1 T2 magnetic resonance imaging scan of papillary carcinoma (arrow)

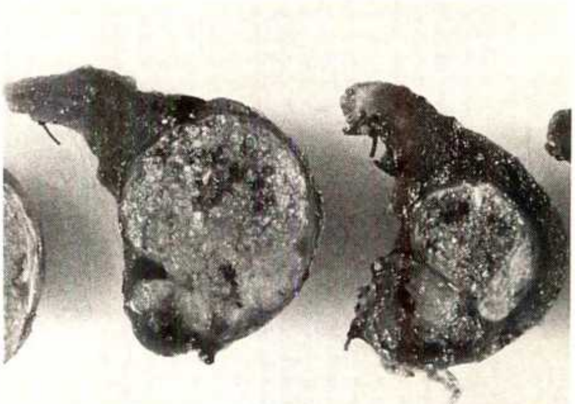

Fig. 2 Gross pathology of papillary carcinoma seen in *Fig. 1*

Based on a presentation to the British Association of Endocrine Surgeons in Bristol, UK, May 1993
Paper accepted 30 August 1995

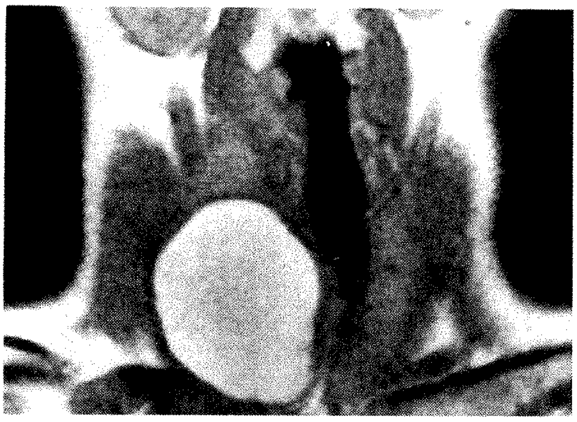

Fig. 3 T1 magnetic resonance imaging scan of cystic follicular adenoma

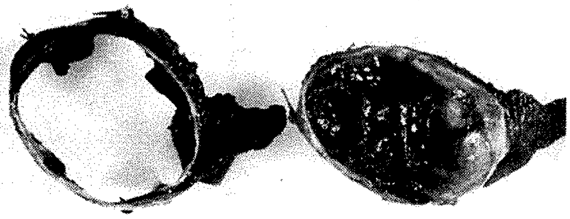

Fig. 4 Gross pathology of follicular adenoma seen in *Fig. 3*

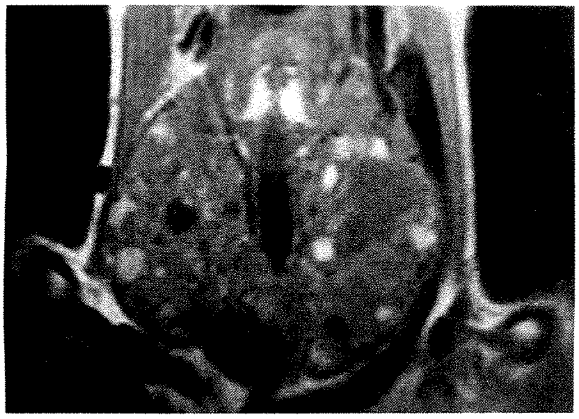

Fig. 5 T1 magnetic resonance imaging scan of colloid goitre

MRI from a follicular adenoma with predominant central cystic degeneration illustrates this point (*Fig. 3*) and gross pathology is shown in *Fig. 4*. In mixed solid or cystic lesions, while there were obvious signal differences between the solid and cystic components, the fluid phase did not yield a consistent appearance on either the T1 or T2 scans. Heterogeneous scans were seen in benign disease as in the multinodular goitre shown in *Fig. 5*. The excellent anatomical definition obtained by the MRI scans was not itself sufficient to permit differentiation between benign and malignant swellings.

Discussion

MRI is a powerful imaging technique which can be performed relatively quickly and safely with no exposure to ionizing radiation. It is, however, the most expensive of the various imaging methods currently available. In this study images of thyroid swellings were obtained which corresponded well with the gross pathology of resected tissue. However, the physical characteristics of thyroid swellings correlate poorly with underlying pathology[5,6] and the incidence of malignancy ranges from 25 per cent in truly isolated solid swellings[3] to 12 per cent in a dominant or cystic isolated swelling[7,8] and less than 4 per cent in a diffuse generalized swelling.

FNAC has reduced the need for operation in patients with thyroid swellings and routine ultrasonography or isotope scanning is no longer appropriate[5]. FNAC, in conjunction with clinical assessment, permits a more conservative approach[1–3]. However, there is a small but significant error rate with false-positive and false-negative reports. An additional imaging modality which reduced this would be useful and it was for this reason that a pilot study was performed. However, there was no consistent hallmark of neoplasia or malignancy and signal strength (whether T1 or T2 weighted) was not consistently different between pathological groups. There is no justification for the routine use of MRI simply to delineate the morphology of a thyroid swelling. Ultrasonographic examination serves this purpose more simply and cheaply. FNAC, however, remains the principal and, in the majority of patients with a thyroid swelling, the only investigation required.

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British Journal of Surgery 1996, **83**, 830–835

Long-term results of a prospective randomized comparison of total fundic wrap (Nissen–Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux

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The importance of the extent of the fundic wrap that encircles the distal oesophagus for the establishment of long-term control of gastro-oesophageal reflux disease (GORD) and for the risk of symptoms after fundoplication was evaluated in a prospective, randomized clinical trial. Of 137 consecutive patients with GORD, 72 were allocated to a semifundoplication (180–200°, Toupet) and 65 to a total fundoplication (360°, Nissen–Rossetti). Dysphagia was more common in the early postoperative period after a total fundic wrap, a difference which disappeared with time. This corresponded to a higher resting tone in the lower oesophageal sphincter area. Seven patients (5 per cent) experienced relapse of GORD during follow-up of more than 3 years. Although no difference in the cumulative relapse rate (5 per cent for Nissen–Rossetti *versus* 6 per cent for Toupet) was found between the two study groups, the total failure rate was higher ($P < 0.05$) among patients who had a Nissen–Rossetti procedure because of a procedure-specific complication: intrathoracic herniation of the fundoplication in five patients caused obstructive symptoms without reflux (four had no posterior crural repair). In addition, symptoms in the form of flatulence were more frequently seen after Nissen–Rossetti fundoplication ($P < 0.05$ at 2 years and $P < 0.01$ at 3 years). Both Nissen–Rossetti and Toupet fundoplication equally well and durably controlled GORD. Fewer symptoms occurred in those having a semifundoplication, both in the early and late postoperative period.

Fundoplication has become the most widely used form of antireflux surgery and the efficacy of the procedure has been established by clinical examination, endoscopic follow-up and oesophageal pH monitoring[1]. However, the prevention of reflux alone does not always provide an optimal result for the patient and persistent symptoms can jeopardize an otherwise excellent result because of dysphagia, inability to belch and vomit, postprandial fullness, bloating, pain and sometimes socially embarrassing flatulence. A number of technical considerations may counteract some of these problems, but available data from controlled clinical trials do not allow firm conclusions[2–7]. The present study was designed to address two clinical questions. First, is it necessary to encircle more than half of the oesophageal circumference by the fundic wrap to control gastro-oesophageal reflux? Second, is a semifundoplication followed by fewer symptoms of gas bloat type than a total fundoplication?

Patients and methods

A total of 137 consecutive patients with chronic gastro-oesophageal reflux disease (GORD) entered the trial (38 per cent men), having a mean age of 53 (range 25–74) years. All patients had a clinical history of GORD (*Tables 1* and *2*, *Fig. 1*). Twenty-two patients had columnar lined oesophagus extending at least 3 cm above the gastro-oesophageal junction. The two study groups were well matched with respect to disease-specific and other relevant clinical parameters. The study protocol was approved by the local ethics committee and informed consent to participate in the study was obtained from each patient.

Some 65 patients were randomized by use of sealed envelopes to a Nissen–Rossetti total fundic wrap and 72 to a semifundoplication according to Toupet[8]. All operations were done through the abdominal route. A posterior crural repair was done only if preoperative barium meal radiography and endoscopy revealed an obvious hiatus hernia and if the operating surgeon considered the hiatus to be markedly wide. In total, 45 per cent of the patients had a crural repair using non-absorbable sutures. In both groups the fundus of the stomach was generously mobilized by dividing the short gastric vessels. The distal oesophagus was exposed through the hiatus by opening the phrenico-oesophageal membrane and a 3–4-cm wide opening made above the hepatic branch of the anterior vagus nerve. The fundus could then be wrapped behind and around the oesophagus without tension. Care was taken to avoid damage to the posterior vagus nerve. A large-bore bougie in the oesophagus was not used during the construction of the wrap. The semifundoplication encircled 180–200° of the oesophageal circumference and the proximal sutures on each side also fixed the fundus to the crura and the lateral margins of the oesophagus. The right suture row was then continued distally with two to three stitches between the fundus and the right margin of the oesophageal wall. The right posterior part of the fundoplication was fixed to the right crus with two to three separate non-absorbable sutures. The left part of the fundoplication was fixed to the left crus by at least two sutures whereafter the left posterior part of the fundoplication was fixed in the same manner as the right side, making the length of the fundus cuff 2–3 cm.

When performing the 360° fundoplication, a more extensive mobilization of the greater curvature of the stomach was done. The anterior part of the fundus encircled the oesophagus and was subsequently reattached to the anterior aspect of the fundus by non-absorbable seromuscular sutures. The oesophageal wall was not included in the stitches and great care was taken to make the fundoplication 'floppy' and about 2–3 cm in length. An index finger could easily be passed between the cuff and the oesophagus.

Clinical assessment

Each patient was interviewed 3, 6, 12 months and then yearly after the operation regarding gastro-oesophageal reflux symptoms as well as those specifically related to the fundo-

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plication procedure. At each assessment, the patient was evaluated by an independent observer. Unless otherwise stated, each symptom was scored from 0 to 3 (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms).

Mild symptoms were those easily controlled e.g. by dietary measures, occasional intake of antacids etc. Severe symptoms included reflux or symptoms occurring after fundoplication which required continuous medical therapy or other therapeutic intervention, or symptoms that caused considerable discomfort to the patient.

Endoscopy

Endoscopic investigation of the oesophagus and the upper gastrointestinal tract was carried out 3 and 12 months, 3 years and 5 years after operation. Olympus video endoscopes or GIF XQ endoscopes were used and the endoscopies were done by an independent investigator who was unaware of the details of the surgical procedure.

Table 1 Clinical characteristics of 137 patients enrolled in the study

	Severity score			
Symptom	0	1	2	3
Heartburn	0	1	5	94
Acid regurgitation	0	2	80	18
Dysphagia	92	8	0	0

Values are percentages. Severity score 0, no complaints; 1, mild complaints; 2, moderate complaints; 3, severe complaints

Table 2 Ambulatory 24-h pH monitoring data

	Percentage of time at pH < 4		
		After operation	
	Before operation ($n = 128$)	6 months ($n = 109$)	3 years ($n = 65$)
Total	15·2(1·1)	5·5(2·4)	2·8(0·6)
Upright	15·5(1·1)	2·2(0·4)	3·4(0·8)
Supine	14·5(1·5)	1·0(0·5)	1·9(0·6)

Values are mean(s.e.m.)

Manometry

Manometry was performed before operation, and at 6 months and 5 years after operation. The pressure characteristics of the gastro-oesophageal junction were measured by a water perfused triple-lumen pressure catheter with three side holes positioned 120° apart. The catheter was connected to a transducer assembly placed at the oesophageal level of the subject in the supine position. Each channel was perfused with 0·5 ml water per min via a low-compliance capillary system. The probe was introduced through the nose in subjects being fasted overnight. A station pull-through technique was used and the probe was withdrawn 0·5 cm each time and kept at each level for at least 30 s or until the recording became stable. The high pressure zone was defined as the mean of the highest pressure plateaux recorded by each of the three ports minus the mean pressure in the gastric fundus measured at the end of expiration. The length of the intra-abdominal part of the high pressure zone was calculated from the pressure profile as the distance from the point of the first stable pressure increase above fundus pressure to the first point of negative pressure to change at inspiration.

Ambulatory 24-h pH monitoring

Ambulatory 24-h pH monitoring was done before operation and during the postoperative follow-up at 6 months and after 3 years as described previously[8]. A monocrystalline antimony pH electrode was passed and secured to the nose with an electrode placed 5 cm above the high pressure zone as located by manometric examination. A reference electrode was attached to the skin of the chest. The pH electrode was calibrated before and after the investigation and the pH data obtained every 4 s were stored in a digital memory. The patients were ambulatory throughout all recordings and were instructed to follow their usual pattern of living. Reflux symptoms, meals including drinking or smoking, and resting periods were recorded in a

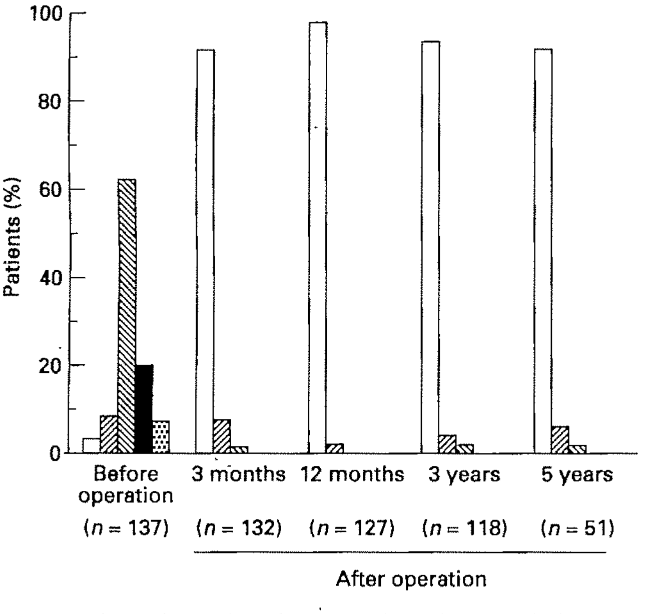

Fig. 1 Endoscopic grading of the oesophageal mucosa before and at different intervals after antireflux surgery. □, Grade 0; ▨, grade 1; ▧, grade 2; ■, grade 3; □, grade 4

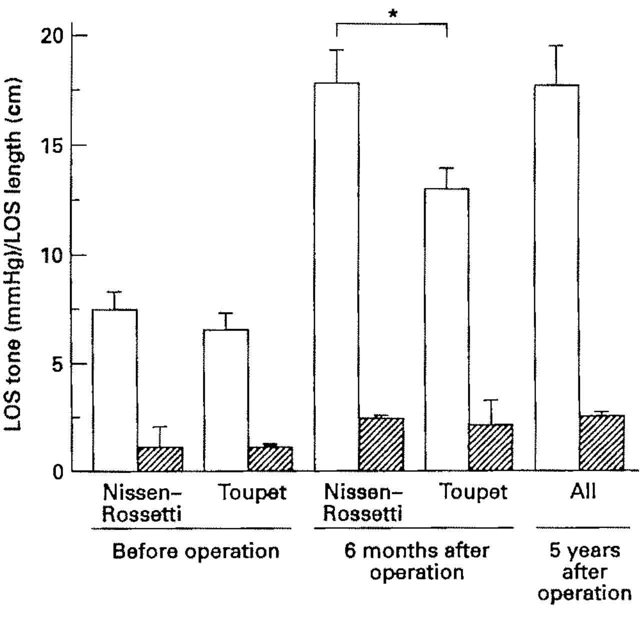

Fig. 2 Mean(s.e.m.) lower oesophageal sphincter (LOS) tone (□) and intra-abdominal length (▨) in patients with gastro-oesophageal reflux disease before operation ($n = 85$) and 6 months ($n = 74$) and 5 years ($n = 13$) after Nissen–Rossetti or Toupet fundoplication. $^*P < 0·01$, Mann–Whitney *U* test

diary by the patients. The pH data and information given in the diary were evaluated manually as well as by computer.

Statistical analysis

Statistical analysis was carried out by applying the Mann–Whitney *U* test and analysis of variance (ANOVA) for repeated measures. All data are presented as mean(s.e.m.).

Results

No serious peroperative or postoperative complications occurred. However, because of peroperative damage to the spleen, splenectomy had to be done in three patients, all of whom were allocated to a Toupet semifundoplication. One of these patients had a prolonged

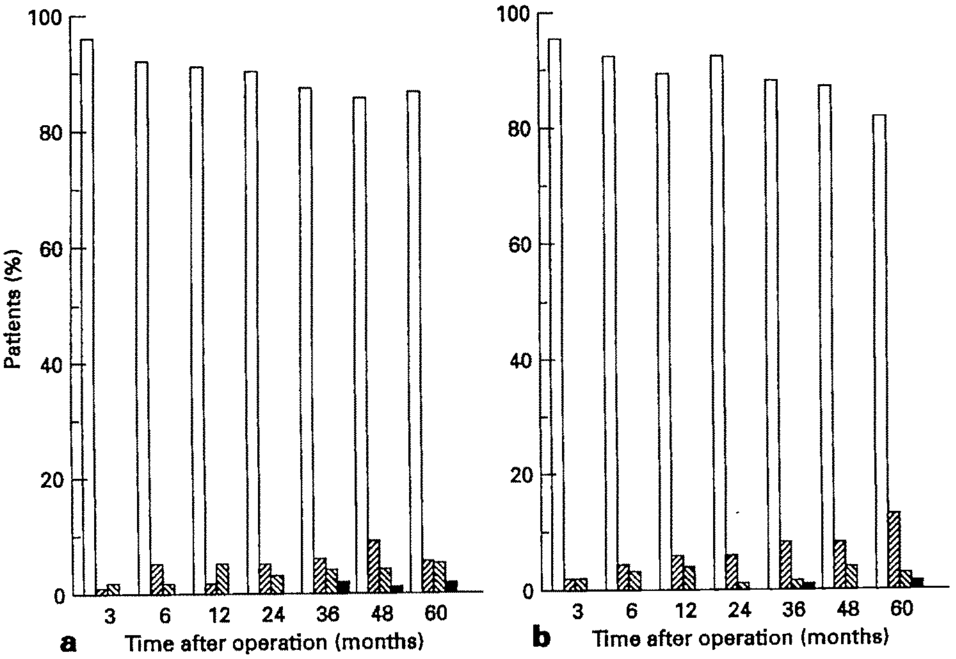

Fig. 3 Major reflux symptoms of a heartburn and b acid regurgitation in patients with gastro-oesophageal reflux disease at different intervals after antireflux surgery. □, No symptoms; ▨, mild; ▩, moderate; ■, severe. There was no difference between the operative groups

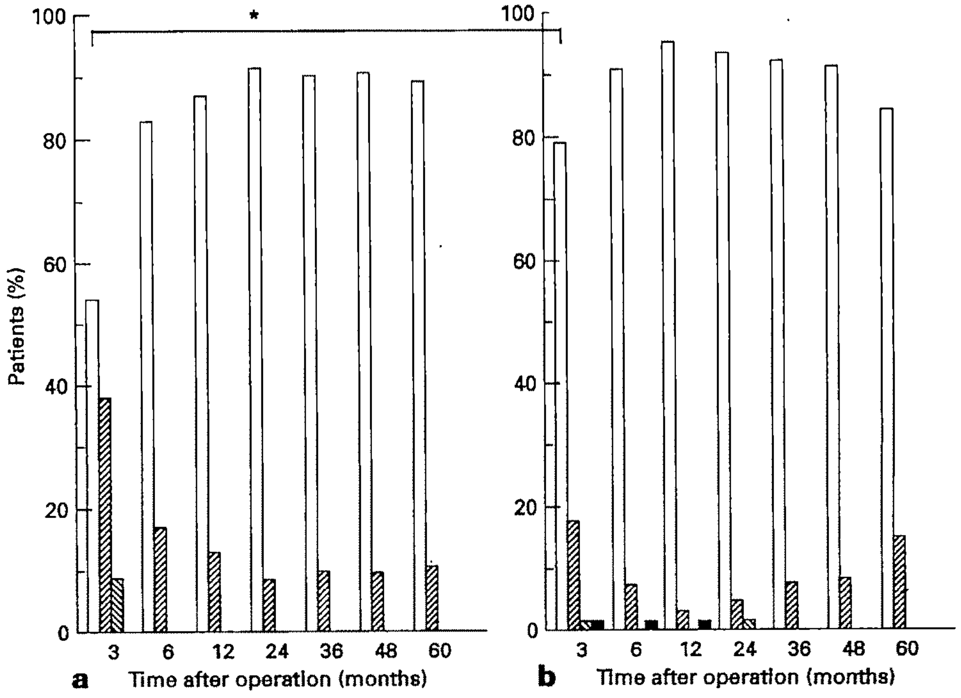

Fig. 4 Postoperative dysphagia after a Nissen–Rossetti and b Toupet fundoplication. □, No dysphagia; ▨, mild; ▩, moderate; ■, severe. $^{*}P < 0.05$, analysis of variance

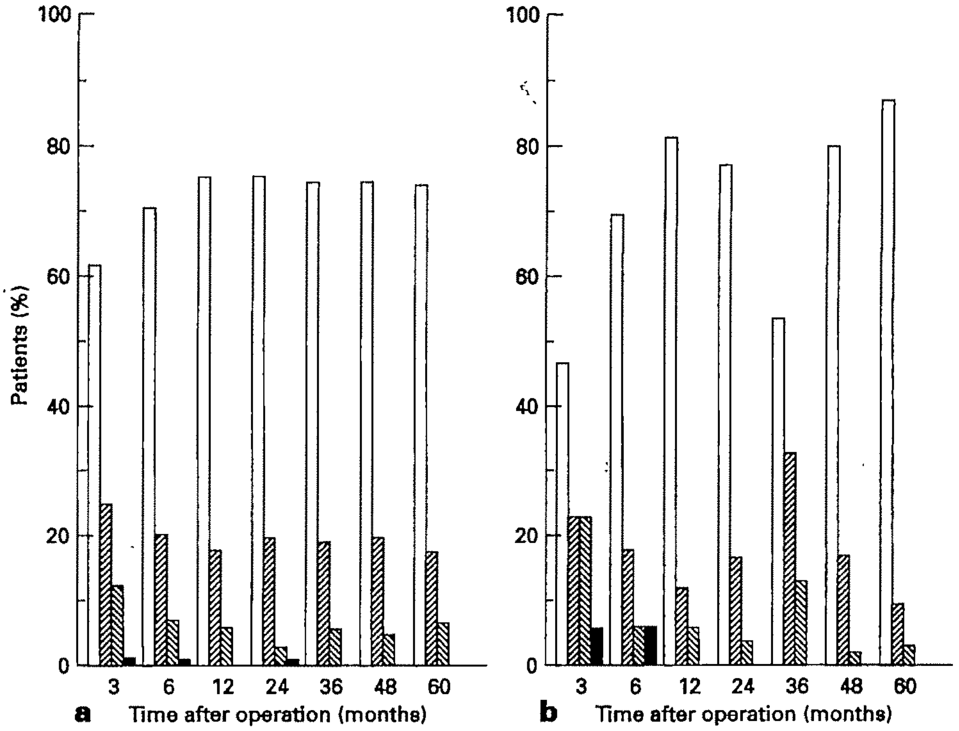

Fig. 5 Postoperative symptoms of a bloating and b postprandial fullness. □, None; ▩, mild; ▨, moderate; ■, severe. There was no difference between the operative groups

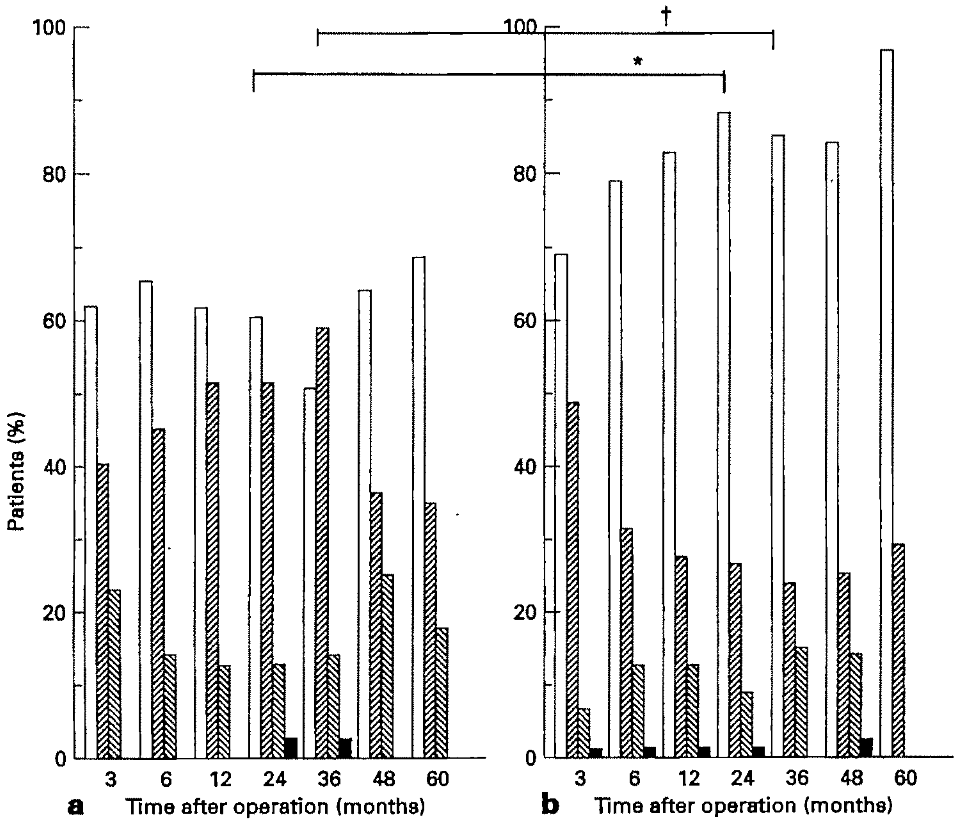

Fig. 6 Postoperative complaints of flatulence after a Nissen–Rossetti and b Toupet fundoplication at different intervals after the operation. □, None; ▩, mild; ▨, moderate; ■, severe. $^{*}P < 0{\cdot}05$, $^{\dagger}P < 0{\cdot}01$, analysis of variance

postoperative course due to an intra-abdominal abscess in the subphrenic space. Another patient suffered from severe respiratory distress after surgery and required a period of artificial ventilation. The minimum follow-up was 3 years and in 62 patients it extended beyond 5 years. During follow-up, two patients died from unrelated diseases and another three were lost to follow-up 1 year or later after operation. At the last follow-up visit none of these patients had evidence of recurrent GORD. Both patients who died had a Nissen–Rossetti fundoplication, whereas two lost to follow-up had a Toupet and one a Nissen–Rossetti fundic wrap.

Preoperative data on the abdominal length and magnitude of the high pressure zone in the gastro-oesophageal junction were available in 85 patients. Mean(s.e.m.) tone was 7·1(0·6) mmHg and the intra-abdominal length 11(0·3) mm. There was no difference in the preoperative sphincter characteristics between the two study groups. At 6 months after operation, the mean(s.e.m.) abdominal length of the high pressure zone had increased to 20·5(1·0) mm and the resting tone to 15·1(0·9) mmHg. After 6 months basal pressure was significantly higher in patients having a total fundic wrap ($P \leq 0.01$; *Fig. 2*). Meaningful comparison is not available yet at 5 years; only 13 patients have been studied with a proper pull-through procedure so far.

A relapse of GORD was defined as recurrent symptoms of similar character (but not necessarily of similar severity) to those assessed before operation and/or endoscopic signs of oesophagitis[8]. The symptoms should be severe enough to require at least intermittent medical therapy and not managed only by modification to lifestyle. Recurrence of reflux occurred in seven patients, four (6 per cent) in the Toupet and three (5 per cent) in the Nissen–Rossetti group (*Fig. 1*). Five of these patients had a relapse within 6 months of operation. The long-term clinical outcome as assessed both clinically, endoscopically and by use of 24-h pH monitoring is illustrated in *Figs. 1* and *3* and *Table 2*. No difference was observed between the two study groups with regard to these variables.

Specific fundoplication symptoms such as inability to vomit were reported by the patients with a similar frequency in both groups (85 per cent), when evaluated after 3 months, and the corresponding incidence at 3 and 5 years was 88 and 90 per cent respectively. However, only 5 per cent of patients stated that inability to vomit exerted a detrimental effect on their quality of life either in the early or late postoperative period. At 3 months after operation, 82 per cent were able to vent air from the stomach and 80 per cent reported a similar ability 3 and 5 years later. Consequently, most patients were able to belch after surgery with no difference between the two procedures. Other symptoms after fundoplication such as dysphagia, postprandial fullness, bloating and flatulence are illustrated in *Figs 4, 5* and *6*. Dysphagia was more frequently reported in patients who had Nissen–Rossetti fundoplication after 3 months ($P < 0.05$), a difference which subsequently disappeared. Several postprandial symptoms were evident in the early postoperative phase but then improved. There was, however, a significant difference between the two groups with respect to complaints of flatulence (*Fig. 6*). Significantly fewer patients who had a Toupet fundoplication complained of flatulence during the follow-up period ($P < 0.05$ at 2 years and $P < 0.01$ at 3 years).

One patient complained of severe gas bloat symptoms after Toupet fundoplication and required reoperation. Five patients who had a 'floppy' Nissen–Rossetti had herniation of the fundoplication into the thoracic cavity, giving rise to symptoms ranging from signs of pure obstruction to postprandial pain, but none had reflux. None of the Toupet group had similar herniation. This complication was diagnosed at variable time intervals after the operation. All these patients have now had successful reoperations. Noteworthy is that only one of these five patients had a crural repair at the primary operation. As a consequence of this, the total failure rate was higher among those allocated to Nissen–Rossetti fundoplication ($P < 0.05$).

Discussion

A number of successful reflux-preventing operations have evolved over the years. Each surgeon uses the procedure that works best in his or her hands, but not every exponent of a technique is as satisfied with the results as the originator[1,9–11]. The majority of studies on antireflux surgery report good to excellent results after various fundoplication operations. Ideally, follow-up after these procedures should be carried out by an independent assessor and/or by means of a detailed pro forma, thus offering objective data[12–14]. Surgeons who undertake antireflux surgery need to agree on standardized operative methods and objective criteria to define success, thereby allowing agreement about classification of anatomical, pathological and endoscopic features of the disease. Information from controlled, randomized clinical trials shows that various fundoplication procedures extensively used in clinical practice result in similar long-term control of reflux symptoms[8,15–18]. Many of the clinical trials carried out so far have enrolled a limited number of patients allowing a significant risk of type II error. There may yet be differences between efficacy and complication rates between various antireflux procedures.

The total fundic wrap (Nissen fundoplication) with its modifications is the method of choice in many centres throughout the world. However, a total fundic wrap may need to be re-evaluated based on the preponderance of postoperative symptoms seen in the present study. This is particularly significant since it was found that the partial fundic wrap according to Toupet controlled reflux equally well and durably when assessed objectively by an independent clinical observer, endoscopy and 24-h pH monitoring. There are reports in the literature documenting a considerably higher failure rate after some antireflux procedures and most failures[19] occur early in the postoperative period, emphasizing the importance of concentrating on technical operative details.

Most fundoplication procedures enhance the basal tone recorded in the lower oesophageal sphincter (LOS)[20]. In this study a higher tone in the high pressure zone was recorded in patients who had a total fundic wrap, which might be responsible for complaints of early postoperative dysphagia in these patients. Unfortunately, there are not yet enough data to establish whether this pressure difference remained after 5 years, although no difference in obstructive symptoms was recorded at that time. The protection of the oesophageal mucosa from exposure to refluxed gastric juice afforded by the LOS depends on its resting pressure, the length exposed to abdominal pressure and the overall length of the high pressure zone. Mechanical incompetence of the cardia can occur when any of these components fails[20,21]. The control of reflux as demonstrated by postoperative 24-h pH monitoring, endoscopy and clinical assessment also suggested that competence of the cardia was durably achieved in patients with a semifundoplication. It is questionable whether an even shorter total fundoplication of 1 cm or less might be followed by fewer symptoms without jeopardizing control of reflux[22].

A fundamental question that has rarely been addressed is the extent to which gas bloat symptoms and other complaints typically seen after fundoplication are present before operation in patients with chronic GORD[12]. It is important to know if preoperative gas bloat symptoms predict an unfavourable outcome of surgery and whether the method of fundic wrap affects these postoperative complaints. The postprandial adverse symptoms which occur after fundoplication are usually mild, and often less severe than preoperative reflux symptoms. Fundoplication procedures impair the ability to belch and thereby to relieve bloating[23]. Inability to belch occurs in about 40 per cent of patients after a total fundic wrap and inability to vomit in 30–90 per cent. Other studies report that many patients are able to vomit after operation, and that this increases with time. There could be concern regarding eventual disruption of the wrap or this may be an example of subsidence of complaints with the passage of time. No controlled, prospective clinical trial has evaluated ability to belch and vomit after semifundoplication or total fundic wrap. A tendency to fewer gas bloat symptoms has been reported after semifundoplication with a short- and long-term follow-up[8,15]. In this study there was a significant advantage in favour of Toupet fundoplication with respect to the occurrence and persistence of flatulence. This difference seemed to increase with the passage of time. The only explanation for this observation is that patients who had a semifundoplication vented air from the stomach more easily than those who had a total fundic wrap.

This study has shown that a partial fundic wrap according to Toupet offers control of reflux disease which is durable and as effective as a total fundic wrap. The former procedure seems to have some advantages in that there were fewer postprandial complaints.

Acknowledgements

The study was supported by a grant from the Swedish Medical Research Council (no. 17X-760).

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British Journal of Surgery 1996, 83, 836–839

Limited operation for gastric cancer in the elderly

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The relationship between operative procedures for treatment of patients with gastric carcinoma and complications was studied with special reference to the age of patients, who were divided into four groups: 50–59 years; 60–69 years; 70–79 years; and over 80 years. Preoperative risk factors that were common in patients over 70 years of age were hypertension and cardiac disease. The selected operative procedures were similar for each age group. However, neither proximal gastrectomy nor reconstruction by jejunal interposition was selected for patients of 80 years and over. In these patients, resection of the neighbouring organs was seldom performed and lymph node dissection was usually limited to the primary and secondary nodes. There was no significant difference in the rate of postoperative complications between groups. Although only limited surgery was performed for patients of 80 years and over, there was no significant difference in age-corrected cumulative survival rate between groups. Therefore, limited resection and/or lymph node dissection may allow safe surgical treatment for patients of 80 years and over with gastric carcinoma, without any negative effect on prognosis.

There are numerous reports of surgical treatment for abdominal disorders in patients over 70 years of age. However, there is little information on operations for stomach cancer in patients aged over 80 years. Lymph node metastasis is a critical factor in the prognosis of stomach cancer, and patients with nodal involvement have a poor clinical course[1]. Extended lymph node dissection has been recommended on the basis of studies of lymphatic flow and nodal spread of cancer cells[2]. For patients with advanced cancer in the upper part of the stomach, the tail of the pancreas and/or spleen are usually resected to remove possible nodal involvement[3]. In cases of direct invasion by gastric cancer, the organs involved are resected[4]. However, it is unclear whether such extended resections should be performed in elderly patients. Although patient survival is the essential aim of surgical treatment, extended surgery sometimes reduces subsequent quality of life.

In this clinic elderly patients are thought to be physically unable to tolerate extended resection and have therefore been treated by limited surgery. The aim of this study was to compare complications and outcome after gastric surgery with respect to age to assess the effect of this policy.

Patients and methods

Among the 2083 consecutive patients who had surgery for gastric carcinoma at this institution, during the 25-year interval from 1968 to 1992, 480 were aged between 50 and 59 years (group 1), 578 between 60 and 69 years (group 2), 341 between 70 and 79 years (group 3) and 43 were more than 80 years old (group 4). These patients were assessed clinically and pathologically according to the criteria of the Japanese Research Society for Gastric Cancer[5]. Young patients of less than 49 years were excluded from the study. Criteria for abnormal findings at preoperative examination were: a haematocrit less than 40·9 per cent and/or haemoglobin level less than 10 g/dl for anaemia; fasting plasma glucose level greater than 140 mg/dl for diabetes mellitus; vital capacity less than 80 per cent, forced expiratory volume during 1 s less than 70 per cent and/or arterial partial pressure of oxygen less than 79 mmHg for pulmonary disease; blood pressure above 160/95 mmHg for hypertension; an abnormal electrocardiogram; serum bilirubin level over 2·0 mg/dl; and serum creatinine concentration over 1·5 mg/dl and/or blood urea nitrogen level over 17 mg/dl for renal disease. Postoperative complications were carefully monitored and patients were followed for a minimum of 1 year after surgery.

Operative procedures were selected after consideration of the stage of tumour, as well as the patient's age and general condition. Almost all patients were treated by a small group of surgeons from this department. Methods of resection included distal, proximal and total gastrectomy. For reconstruction, Billroth I or Billroth II was selected mainly following distal gastrectomy; modified Billroth II, Roux-en-Y or jejunal interposition following total gastrectomy and jejunal interposition after proximal gastrectomy. Extended resection of the stomach and regional lymph nodes was the standard strategy. Even in the elderly, curative resection was always attempted. However, the individual surgeon was responsible for selection of the extent of prophylactic procedures, such as lymph node dissection, splenectomy and pancreatectomy.

Elderly patients aged more than 70 years of age (groups 3 and 4) were compared with those in the other groups (groups 1 and 2) with respect to operative method, morbidity and survival. The cumulative and age-corrected cumulative survival rates of patients were obtained for each age group. As the present study covered a 25-year interval, the cohort life-expectancy table did not include all patients for calculation of age-corrected cumulative survival rates. Statistical analysis was performed by the χ^2 test and the generalized Wilcoxon test.

Results

The most frequent preoperative risk factor identified was hypertension, in 132 patients (9·2 per cent) (*Table 1*). Diabetes mellitus and cardiac disease were found in 79 (5·5 per cent) and 59 (4·1 per cent) patients respectively. Hypertension was significantly more frequent in the elderly, as was cardiac disease. There was no difference in the incidence of other preoperative risk factors between age groups.

A comparison of operative methods revealed that rates of distal and total gastrectomy were similar among the groups (*Table 2*). Proximal gastrectomy was not selected for patients over 80 years. For reconstruction, Billroth I and Billroth II were selected at similar frequencies for

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Paper accepted 3 September 1995

Table 1 Risk factors before operation

	Group 1 (50–59 years) ($n = 480$)	Group 2 (60–69 years) ($n = 578$)	Group 3 (70–79 years) ($n = 341$)	Group 4 (80 years and over) ($n = 43$)
Local complications				
Bleeding	4 (0·8)	14 (2·4)	6 (1·8)	2 (5)
Perforation	2 (0·4)	3 (0·5)	0 (0)	0 (0)
Stenosis	16 (3·3)	16 (2·7)	16 (4·7)	1 (2)
General complications				
Anaemia	14 (2·9)	22 (3·8)	14 (4·1)	4 (9)
Diabetes mellitus	28 (5·8)	32 (5·0)	17 (5·0)	2 (5)
Hypertension	21 (4·4)	58 (1·0)	46 (13·5)*	7 (16)*
Cardiac disease	12 (2·5)	23 (4·0)	18 (5·3)†	6 (14)*‡
Pulmonary disease	10 (2·1)	17 (2·9)	6 (1·8)	2 (5)
Liver dysfunction	12 (2·5)	10 (1·7)	5 (1·5)	1 (2)
Renal dysfunction	2 (0·4)	5 (0·9)	4 (1·2)	2 (5)
Other	44 (9·2)	69 (11·9)	46 (13·5)	8 (19)

Values in parentheses are percentages. *$P < 0·001$, †$P < 0·05$, *versus* group 1; ‡$P < 0·01$ *versus* group 2 (χ^2 test)

Table 2 Method of gastric resection

	Group 1 (50–59 years) ($n = 480$)	Group 2 (60–69 years) ($n = 578$)	Group 3 (70–79 years) ($n = 341$)	Group 4 (80 years and over) ($n = 43$)
Operative resection				
Distal gastrectomy	364 (75·8)	447 (77·3)	236 (69·2)	35 (81)
Proximal gastrectomy	25 (5·2)	29 (5·0)	17 (5·0)	0 (0)
Total gastrectomy	91 (19·0)	102 (17·6)	61 (17·9)	8 (19)
Reconstruction				
Billroth I	209 (42·1)	236 (40·8)	120 (35·2)	17 (40)
Billroth II	155 (32·3)	211 (36·5)	116 (34·0)	17 (40)
Modified Billroth II	57 (11·9)	72 (12·5)	50 (14·7)	7 (16)
Roux-en-Y	9 (1·9)	11 (1·9)	4 (1·2)	0 (0)
Interposition	22 (4·6)	34 (5·9)	16 (4·7)	0 (0)
Other	19 (4·0)	23 (4·0)	8 (2·3)	2 (5)
Extended resection				
None	336 (70·0)	450 (77·9)	221 (64·8)	35 (81)
Pancreas	67 (14·0)	77 (13·3)	47 (13·8)	1 (2)
Spleen	89 (18·5)	98 (17·0)	59 (17·3)	2 (5)*
Liver	2 (0·4)	4 (0·7)	4 (1·2)	0 (0)
Transverse colon	8 (1·7)	12 (2·1)	3 (0·9)	0 (0)
Lymph node dissection				
N1 alone	70 (14·6)	102 (17·6)	37 (10·9)	15 (35)†‡
N1, N2 only	271 (56·5)	345 (59.7)	218 (63·9)	26 (60)
N1, N2, N3	139 (29·0)	131 (22·7)	53 (15·5)	2 (5)†

Values in parentheses are percentages. N1, perigastric nodes; N2, nodes along the left gastric and common hepatic arteries and around the coeliac artery; N3, nodes at the splenic hilum, along the splenic artery, in the hepatoduodenal ligament, behind the head of the pancreas and at the root of the mesentery. *$P < 0·05$ *versus* groups 1, 2 and 3; †$P < 0·01$ *versus* groups 1 and 2; ‡$P < 0·001$ *versus* group 3 (χ^2 test)

each group. However, jejunal interposition was not used in patients over 80 years. Extended resection was similarly infrequent in the elderly, and the extent of lymph node dissection was limited. Only two patients in group 4 had extended lymph node dissection which included the primary, secondary and tertiary nodes. The rate of extended lymph node dissection was significantly lower in group 4 than in groups 1 and 2.

With regard to evaluation after surgery, the rates of curative operation were 86·5 per cent in group 1, 85·5 per cent in group 2, 88·9 per cent in group 3 and 84 per cent in group 4, with no significant differences identified. Histological examination revealed that there were no significant differences in the clinical stage of disease between groups.

Local complications were significantly more common in the elderly (*Table 3*). The incidences of anastomotic leaks and of intraperitoneal abscess were higher in group 4. However, the incidence of other local complications was similar between age groups. There were no significant differences in the rate of general complications. The operative mortality rates were 4·2 per cent ($n = 20$) in group 1, 4·7 per cent ($n = 27$) in group 2, 5·3 per cent ($n = 18$) in group 3 and 5 per cent ($n = 2$) in group 4.

The cumulative survival rate for each age group was calculated by an actuarial method (*Fig. 1*). Five- and

Table 3 Complications after surgery

	Group 1 (50–59 years) ($n = 480$)	Group 2 (60–69 years) ($n = 578$)	Group 3 (70–79 years) ($n = 341$)	Group 4 (80 years and over) ($n = 43$)
Local complications				
None	416 (86·7)	472 (81·7)	266 (78·0)	32 (74)*
Anastomotic leak	20 (4·2)	37 (6·4)	20 (5·9)	4 (9)
Peritoneal abscess	2 (0·4)	6 (1·0)	2 (0·6)	2 (5)
Bleeding	5 (1·0)	5 (0·9)	2 (0·6)	0 (0)
Stenosis	22 (4·6)	19 (3·3)	10 (2·9)	1 (2)
Fistula	1 (0·2)	2 (0·3)	0 (0)	0 (0)
Ileus	13 (2·7)	14 (2·4)	4 (1·2)	1 (2)
Other	8 (1·7)	16 (2·8)	10 (2·9)	3 (7)
General complications				
None	410 (85·4)	475 (82·2)	266 (78·0)	39 (91)
Cardiac failure	2 (0·4)	6 (1·0)	3 (0·9)	1 (2)
Lung disease	17 (3·5)	41 (7·1)	14 (4·1)	0 (0)
Liver dysfunction	36 (7·5)	31 (5·4)	13 (3·8)	1 (2)
Renal failure	1 (0·2)	2 (0·3)	2 (0·6)	0 (0)
Shock	1 (0·2)	5 (0·9)	2 (0·6)	0 (0)
Disseminated intravascular coagulation	2 (0·4)	6 (1·0)	2 (0·6)	0 (0)
Other	15 (3·1)	18 (3·1)	12 (3·5)	2 (5)

Values in parentheses are percentages. $^*P < 0·05$ *versus* group 1 (χ^2 test)

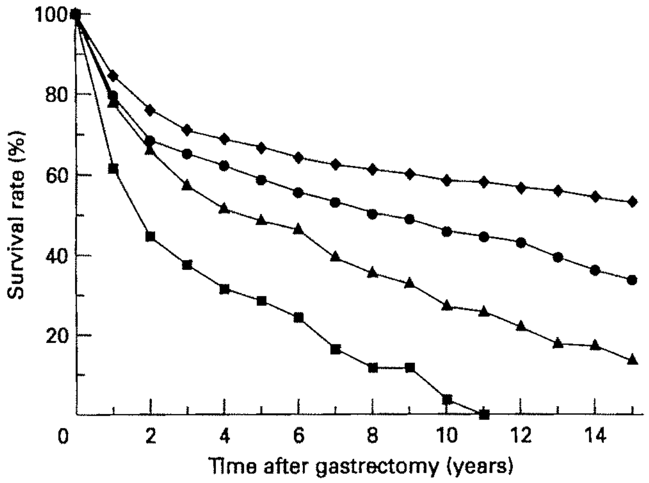

Fig. 1 Cumulative survival of patients with gastric cancer classified by age into four groups: 50–59 years (group 1; $n = 480$) (◆); 60–69 years (group 2; $n = 578$) (●); 70–79 years (group 3; $n = 341$) (▲); and over 80 years (group 4; $n = 43$) (■). There were significant differences in postoperative survival rates among the groups

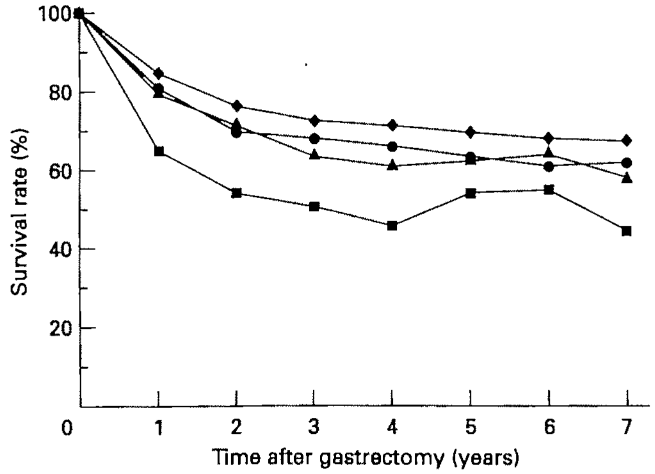

Fig. 2 Age-corrected cumulative survival of patients with gastric cancer who were classified by age into four groups: 50–59 years (group 1; $n = 392$) (◆); 60–69 years (group 2; $n = 514$) (●); 70–79 years (group 3; $n = 301$) (▲); and over 80 years (group 4; $n = 32$) (■). There were no significant differences in postoperative survival rates among the groups

10-year survival rates were 66·3 and 59·0 per cent in group 1, 58·3 and 46·0 per cent in group 2, 48·6 and 27·4 per cent in group 3 and 28 and 4 per cent in group 4 respectively. There were significant differences in postoperative survival times between groups (group 1 *versus* group 2, $P < 0·01$; group 2 *versus* group 3, $P < 0·01$; group 3 *versus* group 4, $P < 0·05$). The age-corrected cumulative survival rate of each group was calculated using data for 1981 published by the Japanese Ministry of Health and Welfare (*Fig.* 2). There were no significant differences in age-corrected survival rate between groups. Five-year age-corrected cumulative survival rates were 68·9 per cent in group 1, 63·2 per cent in group 2, 62·1 per cent in group 3 and 53 per cent in group 4.

Discussion

There are no established criteria as to the age at which a patient should be considered 'elderly' in relation to surgical treatment. Among patients with gastric cancer, the proportion over 70 years of age has been increasing in this clinic[6]. Decreasing surgical mortality has encouraged surgeons to operate on elderly patients with gastric cancer[7]. Morel *et al.*[8] reported that patients over 80 years of age tolerate surgical resection of tumours of the gastrointestinal tract. In the present study, operative mortality rate was similar in elderly patients.

Radical gastrectomy may not be justified in elderly patients. Bandoh *et al.*[9] reported that 90 per cent of patients over 70 years of age had preoperative risk factors. Elderly patients in this study had a relatively high incidence of preoperative risk factors, in particular hypertension and cardiac disease. Although local complications were common in patients aged 80 years and over, there was no significant relationship between the incidence of general complications and age. Similar operations were performed on patients aged 70–79 years, compared with those aged 50–69 years. Patients aged 70–79 years are physiologically similar to those aged under 70 years. Patients aged 80 years and over were treated by limited surgery, and local complications after operation were not infrequent. Age has previously been thought to be a major determinant with respect to postoperative complications and mortality[10]. Bittner *et al.*[7] reported that the recent decline in surgical mortality after gastrectomy in patients above 70 years of age was related to the decreasing rate of splenectomy. Data from this clinic showed that 70 per cent of patients over 70 years of age returned to normal life within 1 year of surgery[11]. However, general health was poorer compared with younger patients[12]. In this study, the postoperative complication rate was similar for both total and distal gastrectomy in elderly patients. Total gastrectomy may be the procedure of choice for elderly patients, rather than proximal gastrectomy with jejunal interposition, because of the simplicity of the operation. Limitations to the extent of surgery in elderly patients may be more important than the resected area of the stomach.

Gastrectomy has adverse effects on patient nutrition after surgery. There was a significant effect of age on cumulative survival rate but this was abolished when age-corrected cumulative survival rates were calculated. Thus, it appears that elderly patients are no longer a special group when the indications for gastrectomy are considered. For gastric surgery, 'elderly' patients may perhaps now be deemed to be those over 80 years of age. Although surgeons must select operative procedures on an individual basis the present policy of less radical surgery for patients over 80 years old seems justified by these results.

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British Journal of Surgery 1996, 83, 840–844

Risk of further ulcer complications after an episode of peptic ulcer bleeding

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To identify the risk factors for developing recurrent ulcer complications after recovery from an episode of peptic ulcer bleeding 611 patients admitted with peptic ulcer bleeding were studied. Some 557 (91 per cent) were discharged without operation. A total of 22 patients were lost to follow-up and five were excluded as maintenance H_2 blockers were required. Of the remaining 530 patients at risk, 169 (32 per cent) developed another complication (166 bleeding, three perforations) over a median follow-up period of 36 months. Patients with duodenal ulcers at the time of bleeding, previous history of peptic ulcer, previous bleeding, history of dyspepsia longer than 3 months, and a short interval between previous ulcer complications and the index bleed were more likely to develop further complications. Sex, age, smoking, coexisting illness, non-steroidal anti-inflammatory drugs intake and time taken to achieve ulcer healing had no predictive value.

Haemorrhage is the most common complication of peptic ulcer disease. Although bleeding stops spontaneously in most cases, some patients require endoscopic intervention or operation to achieve haemostasis[1]. Some 90–95 per cent of these patients may be discharged without operation and 75–85 per cent of ulcers would heal after short courses of H_2 blockers[2], but these treatments do not affect the ulcer diathesis. Data concerning the outcome in those patients who have no long-term modification of their ulcer diathesis are lacking. The aim of the present study was to determine the predictive value of various factors on the risk of developing recurrent ulcer complications after an episode of bleeding.

Patients and methods

All patients presenting with symptoms and signs of upper gastrointestinal bleeding between 1985 and 1987 were admitted and managed by a combined gastroenterology team with a policy of early endoscopy within 24 h of admission. Demographic data, ulcer history, dyspeptic history, previous ulcer complications, coexisting illness and non-steroidal anti-inflammatory drug (NSAID) intake were prospectively collected and entered into a database using an IBM-compatible computer system. Patients with a high risk of rebleeding in hospital were given aggressive endoscopic treatment and monitored closely in designated surgical gastroenterology wards. Patients were managed according to a preset protocol that operation would be offered if they had uncontrolled bleeding, rebleeding in hospital or a transfusion requirement of more than 8 units during the admission. All patients not undergoing operation were followed up in a combined ulcer clinic staffed by both surgeons and physicians. The policy at the time of study was to treat the ulcers with H_2 blockers until healing was documented by endoscopy. H_2 blockers were then prescribed for a further 6 weeks at maintenance dose, and treatment then ceased. Long-term maintenance was recommended in selected cases only. These patients were accumulated before the availability of *Helicobacter pylori* testing in this unit and so these data were unavailable.

At review, patients were identified by data retrieval from the database. Clinic notes were examined and, if necessary, interviews were conducted by telephone by a research nurse to determine whether an ulcer complication (bleeding, perforation or stenosis) had occurred during the follow-up period. All follow-up information was added to the database file for statistical analysis. Patients were stratified according to age, sex, smoking habit, NSAID intake, site of ulcer, stigmata of recent haemorrhage, previous ulcer history, previous bleeding, dyspeptic history, coexisting illness, time to achieve healing and interval between previous complications and current index bleed. The Kaplan–Meier life table, log rank test and Cox multivariate regression model were employed to determine the predictive value of these variables. The relative complication rate (RCR) at 2 years, defined as the ratio of probability of developing complications at 2 years after admission of the groups being compared, was also estimated for each variable.

Results

Between September 1985 and January 1987, 611 patients were admitted for peptic ulcer bleeding as confirmed by endoscopy. There were 426 patients with duodenal ulcers, 147 with gastric ulcers and 38 with combined gastric and duodenal ulcers. *Fig. 1* shows the outcome in these 611 patients. Five (0·8 per cent) died and 49 (8 per cent) underwent surgical intervention at the same admission. Three died despite operative treatment for ulcer haemostasis (operative mortality, 6 per cent). Another five patients were excluded because they had been subsequently put on long-term H_2-receptor antagonists after discharge. In the remaining 552 patients, 79 refused repeat endoscopy or defaulted on the first follow-up, but 57 of these developed further complications and returned to hospital. Therefore, only 22 patients were lost to follow-up and data for them were not available for analysis. Over a median follow-up period of 36 (range 1–55) months, 169 (32 per cent) of the 530 patients developed recurrent complications, which consisted of rebleeding in 166 and perforations in three. Of these 169 patients, 19 underwent emergency surgery, 33 had semielective operations, and ten were prescribed long-

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term H_2 blocker maintenance. Two patients died during the episode of recurrent complication. Among those without recurrent complications, seven non-healing and two recurrent ulcers were identified and these patients underwent elective anti-ulcer surgery. *Table 1* shows the characteristics of the 530 patients.

Kaplan–Meier life table analysis together with univariate log rank test revealed that five factors were associated with a significantly higher risk of recurrent complications after recovery from an episode of ulcer bleeding (*Table 2*). These were: (1) patients with duodenal rather than gastric ulcer ($P = 0{\cdot}04$, RCR = 2·94); (2) previous history of dyspepsia for more than 3 months ($P = 0{\cdot}05$, RCR = 1·65); (3) previous history of peptic ulcer disease ($P = 0{\cdot}003$, RCR = 2·21); (4) previous ulcer bleeding ($P < 0{\cdot}001$, RCR = 2·02); and (5) an interval of

Table 1 Characteristics of patients

No. of patients	530
Median (range) age (years)	48 (5–91)
Sex (M:F)	380:150
Median (range) length of follow-up	36 (1–55)
NSAID (yes:no)	97:433
Smoking (yes:no)	157:373
Coincidental disease (yes:no)	146:384

NSAID, non-steroidal anti-inflammatory drug

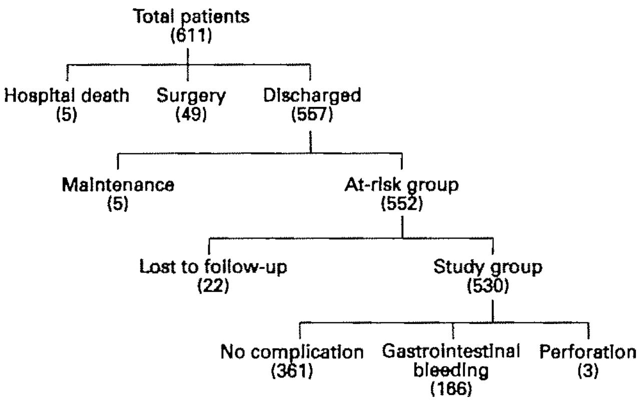

Fig. 1 Outcome of patients admitted for peptic ulcer bleeding between 1985 and 1987 in the Prince of Wales Hospital

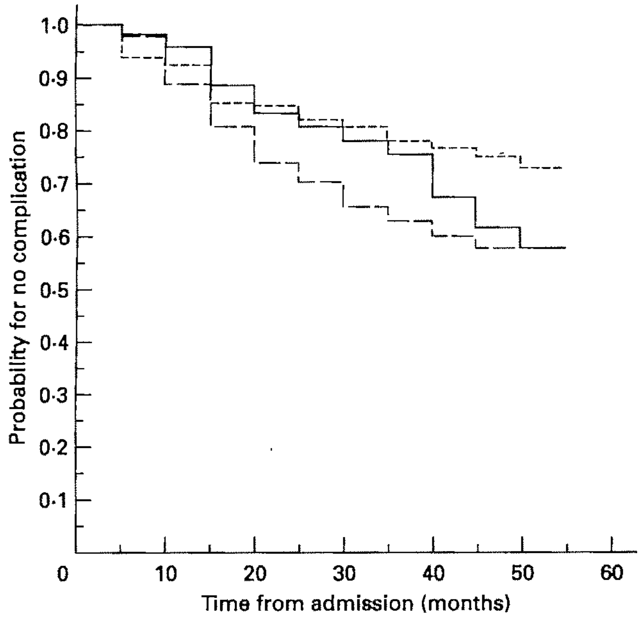

Fig. 2 Life table for patients with gastric ulcer (– – – –), duodenal ulcer (————) and both gastric and duodenal ulcers (———)

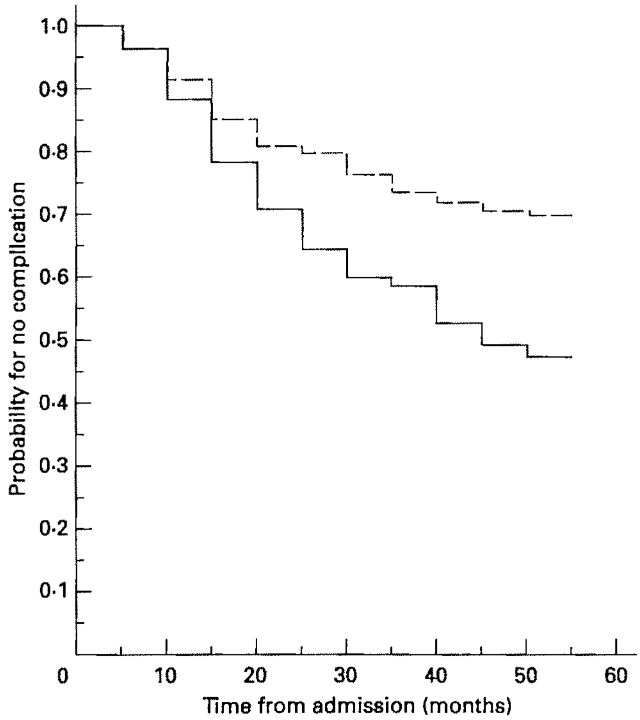

Fig. 3 Life table for patients with (————) and without (– – –) previous ulcer complication

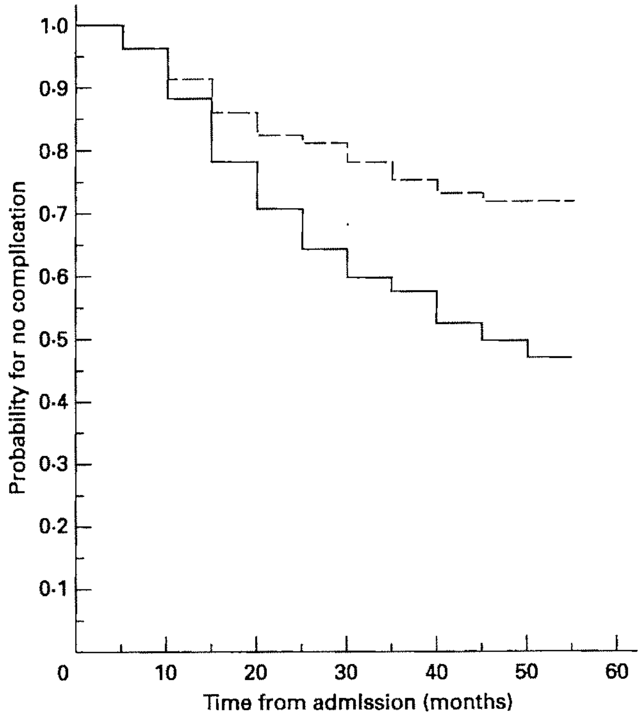

Fig. 4 Life table for patients with (————) and without (– – – –) previous history of ulcer

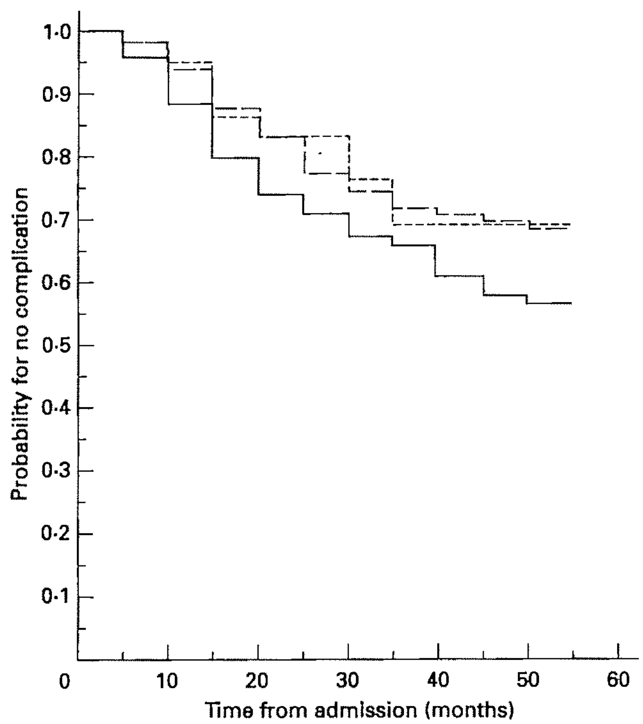

Fig. 5 Life table for patients with short and long dyspeptic history. ————, no history; – – – – –, history for less than or equal to 3 months; ———, history for more than 3 months

Table 2 Summary table

Variables	*P**	*P*†
Age	0·164	n.s.
Sex	0·164	n.s.
Smoking	0·694	n.s.
NSAID	0·227	n.s.
Site of ulcer (duodenal *versus* gastric ulcer)	0·04‡	0·041‡
Dyspeptic history (more than 3 months)	0·05‡	0·924
Previous ulcer	0·003‡	0·18
Previous ulcer bleeding	<0·001‡	0·002‡
Interval from last complication (less than 2 years)	0·013‡	0·043‡
SRH	0·175	n.s.
Coincident disease	0·522	n.s.
Time for healing	0·695	n.s.

*Log rank test; †Cox multivariate regression; ‡significant. n.s., Not significant; NSAID, non-steroidal anti-inflammatory drug; SRH, stigmata of recent haemorrhage

less than 2 years between the previous bleeding and the index bleed ($P = 0{\cdot}013$, RCR = 1·70). *Figs 2–6* are the life-table analyses for these five predictive factors. When the data were further analysed with the multivariate regression model, only duodenal ulceration, history of previous bleeding and a short interval from previous bleeding could independently predict further complications (*Table 2*). Factors such as age, sex, smoking, NSAID consumption, duration of ulcer treatment, intercurrent medical diseases and endoscopic stigmata of recent haemorrhage did not have any significant predictive value for recurrent ulcer complications in either analysis model.

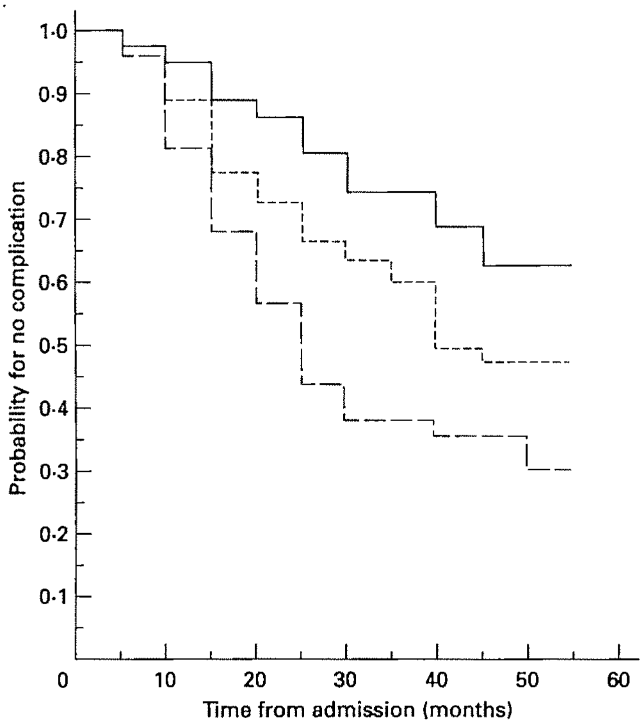

Fig. 6 Life table for patients with short and long intervals between last and index bleeding. Recent complication: ————, less than 2 years; – – – – –, 2–4 years; ———, more than 4 years

Discussion

Although the risk factors for acute ulcer rebleeding in hospital are well recognized[3–5], the pattern of recurrent ulcer complications after complete ulcer healing has been less well studied. It is important to identify the high-risk group among patients who present with ulcer bleeding because further complications may be life threatening. Although it is generally held that definitive ulcer surgery should be performed for patients with more than three episodes of bleeding there have been few data to support this view. One recent randomized, double-blind control study has confirmed the safety and effectiveness of long-term maintenance H_2-receptor blocker in reduction of recurrent ulcer bleeding[6]. However, to give life-long non-selective maintenance therapy to all patients who present with peptic ulcer bleeding is very expensive. It is, therefore, imperative to identify those subjects at high risk so that acid reduction surgery or long-term acid suppression treatments can be prescribed more rationally.

Several factors were predictive for recurrent complications in this study. Contrary to other studies[7], patients with duodenal ulcers were more prone to developing further ulcer complications when compared with those with gastric ulcers. The reason for this is unclear but may relate to the use of different diagnostic tools. Many shallow ulcers could have been missed in the past when barium meal was the gold standard for diagnosis but, with flexible endoscopy, shallower lesions of considerably smaller size can be identified. It is likely that these results have reflected the true natural history of different types of peptic ulcers after an episode of bleeding.

Previous studies have also shown that frequent ulcer relapse and a long history of severe symptoms were associated with a higher incidence of delayed ulcer healing and early relapse[8,9]. In this study, however, the interval between bleeding episodes was more predictive of recurrent complications. While both the frequency and the interval between bleeding episodes are a reflection of the ulcer diathesis, the interval is probably more indicative of the tendency to recurrence. The authors arbitrarily chose 2 years after bleeding to stratify patients because ulcers recur most commonly in the first 2 years after treatment[10,11].

Certain other findings in this study contrast with other reports. First, the association between NSAID use and ulcer bleeding is less marked in these patients. In Western countries NSAIDs play a significant role in the causation of gastroduodenal ulcers and ulcer-related complications[12–14]. The majority of patients in these studies were long-term NSAID users but most of the patients in this study were short-term users who took the drugs inadvertently for non-specific arthralgia, fever or headache. In addition, NSAID-induced ulceration is a problem mainly in patients aged 65[15,16] or more, whereas the mean age of the patients in this study was only 48 years. Second, smoking was incriminated as the cause of poor ulcer healing and early relapse in other studies[17–19]. Increased basal acid secretion[20], decreased pancreatic bicarbonate secretion[21] and increased serum pepsinogen 1 secretion[22] are postulated to be the mechanisms involved. Abstinence from smoking is associated with fewer ulcer relapses[5]. Surprisingly, it was not possible in this study to identify a significant association between smoking and recurrence of ulcer complications, possibly because of changes in smoking habits after the bleeding episode. The low percentage of smokers (30 per cent) and NSAID use (20 per cent) among these patients may be another reason for the lack of correlation.

There is strong evidence that duodenal ulcers and non-NSAID-induced gastric ulcers are associated with antral *Helicobacter* infection[23–25]. Ulcer healing can even be achieved by eradication of *H. pylori* alone without antiacid treatment[26]. In the National Institutes of Health Consensus Statement in 1994, eradication of *H. pylori* has been demonstrated to be effective in reducing the risk of ulcer recurrence to less than 10 per cent in 1 year[27]. However, whether *H. pylori* eradication prevents further complications in those with a history of bleeding is unknown, although it would be logical to assume that complications will not occur if the ulcer does not recur. However, several studies have already reported significant reduction in bleeding relapse following *H. pylori* eradication[28–30]. These series are, however, small and the follow-up period was relatively short.

In summary, patients with a bleeding duodenal ulcer associated with a previous history of bleeding, and especially a short interval between the bleeding episodes, are more likely to develop recurrent complications. It is suggested that if a patient has more than one of these three risk factors, and if he/she is *Helicobacter* negative, long-term H_2-receptor blockers or definitive acid-reducing surgery should be seriously considered.

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European Digestive Surgery

European Digestive Surgery (EDS) is a new group of surgeons committed to raising the profile of gastrointestinal surgery in Europe. This will be achieved in three areas: (1) integration of gastrointestinal surgery as a united body in major European meetings; (2) an educational programme bringing together the best of European digestive surgery; and (3) support for digestive surgical research.

European Meetings. EDS is a new society, but it is not a new meeting. EDS will meet at existing major international meetings within Europe and should allow digestive surgeons to focus their travelling commitments and scientific activities. Gastrointestinal surgeons need to talk to each other because there are many problems which spread across colorectal, pancreaticobiliary and oesophageal surgery. They also need to talk to medical gastroenterologists, and to present digestive surgery on a broad front.

Education. EDS will promote high-quality educational courses in all aspects of gastrointestinal surgical disease. Already three such courses have been organized dealing with standard treatment of pancreatic diseases (Madgeburg; December 1995), advances in pancreatic diseases (Athens, March 1996) and gastro-oesophageal reflux disease (Berne, May 1996).

Research. Through the generous sponsorship of the pharmaceutical industry, EDS is able to offer up to ten research fellowships to pay the salary of promising young researchers active in surgical gastroenterology. These fellowships will be allocated on a competitive basis to encourage high-quality collaborative work, and raise the profile of surgical gastroenterological research. Further details of these awards will be announced shortly.

First general meeting. The first annual meeting of EDS will take place in November 1996, during the United European Gastroenterology Week meeting in Paris. There will be a scientific programme covering all areas of digestive surgery, and an election will be held for officers and council members. The Society has established a transitional board to manage its affairs until the elected council can take over. Transitional board members are indicated on the list of founder members.

Further information about EDS can be obtained from members. Applications for membership should be made to European Digestive Surgery, c/o Karger AG, Allschwilerstrasse 10, PO Box, CH-4009 Basel, Switzerland.

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British Journal of Surgery 1996, 83, 845–846

Short note

Endoscopic perforation in unsedated patients undergoing endoscopy

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The use of sedation for upper gastrointestinal endoscopy varies greatly. It is uncommon in Scandinavia and Japan, whereas other European endoscopy units employ sedation as a routine. Much has been written about the danger of adverse cardiopulmonary events such as oxygen desaturation, induced by endoscope insertion and/or sedation[1]. Serious complications are, however, very rare and the need for monitoring has been refuted[2].

A much greater hazard is perforation, with reported mortality rates of up to 48 and 62 per cent[3], and an incidence of at least 0·03 per cent[4]. A recent report by Quine *et al.*[5] gave a perforation rate of 0·05 per cent in a collected series of 14 149 upper gastrointestinal endoscopies. The present study analysed the experience from one endoscopy unit which routinely uses unsedated endoscopy. Oxygen saturation monitoring is not employed and oxygen supplementation is given on clinical grounds only.

Patients and methods

This endoscopy unit serves a primary population of 300 000 people. The hospital is the referral centre for an additional half a million people; 3000 oesophagogastroduodenoscopies are performed per annum. Since 1990 all endoscopic findings and events have been recorded in a computer-based endoscopy database which can be searched easily and comprises all flexible endoscopy of the upper gastrointestinal tract in the district.

Results

At 1 May 1995 the database contained the results of 13 639 procedures; these data form the study material. Standard endoscopes were used. Sedation with midazolam 2·5–5 mg was used only if intubation was difficult; the sedation rate was 2·1 per cent. There were no serious adverse cardiopulmonary events, and only two perforations (0·015 per cent). Both perforations were induced by consultant surgical endoscopists. Patient demographics and endoscopist status are given in *Table 1*.

One perforation was in an 81-year-old woman referred for laser treatment of a mid-oesophageal carcinoma. The perforation occurred during sedated (midazolam 2·5 mg) laser treatment in the tumour area; it was detected immediately and the patient was brought to the operating room. She had an oesophageal resection with a gastric pull-up, and was discharged after 27 days. At 5 years after operation the patient is still doing well with no recurrence.

The other perforation occurred in the cervical oesophagus of a 77-year-old woman undergoing unsedated diagnostic endoscopy for swallowing difficulties. The patient also underwent operation; the right pleura was drained and she made a complete, if protracted, recovery after 6 weeks in hospital. No oesophageal or gastric abnormality was seen on subsequent radiological examination.

Discussion

Informed patients readily accept unsedated endoscopy with only throat analgesia[6]. The perforation rate in the present series was only one-third that of a large recent study[5]. The same types of endoscopes were used and endoscopist experience seemed to be the same in both series. One notable difference is that patients in the present series were unsedated, but other differences may also have contributed, such as patient mix and age as well as assistant experience.

These data indicate that unsedated endoscopy is also safe in terms of a low perforation rate. Quine and coworkers[5] point out that inexperience may be one factor contributing to perforation. Unsedated endoscopy reduces the incidence of possibly fatal complications.

Paper accepted 21 September 1995

Table 1 Summary of the endoscopy database

	Total no. of procedures ($n = 13\,639$)	Intubation failure ($n = 100$)	Other failure (inability to keep air, gastric retention, etc.) ($n = 123$)	Operative endoscopy (dilatation, laser treatment, polypectomy) ($n = 234$)
Performed by consultant endoscopist (%)	47	42	44	76
Sex ratio (M:F)	7071:6568	43:57	59:64	157:77
Age (years)*				
<40	2083	66		9
41–50	2355	36		73
>50	9155	121		152
No. of perforations	2	1		1

*Age not given for 46 patients

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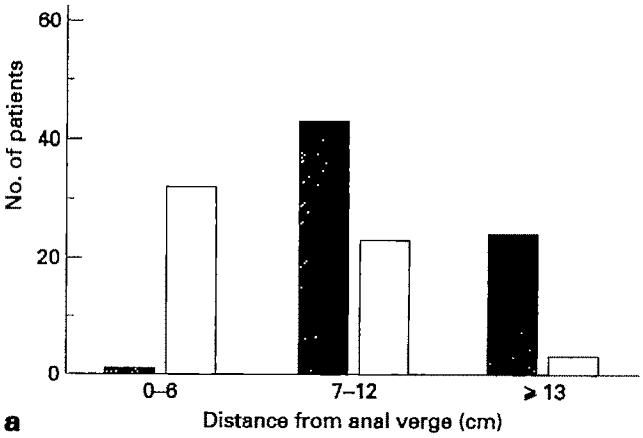
Corrigenda

P. M. Sagar and J. H. Pemberton. Surgical management of locally recurrent rectal cancer. *British Journal of Surgery* 1996; 83: 293–304.

The paragraph appearing under *Fig. 1* on page 299 should read: 'Five-year actuarial local control and disease-free survival rates in 13 patients after sacrectomy with clear surgical resection margins were 62 and 54 per cent respectively[149].

G. Arbman, E. Nilsson, O. Hallböök and R. Sjödahl. Local recurrence following total mesorectal excision for rectal cancer. *British Journal of Surgery* 1996; 83: 375–379.

Fig. 2a should have appeared as follows:



British Journal of Surgery 1996, 83, 847–864

Surgical Infection Society of Europe Abstracts

The following abstracts (papers and posters) were presented at the 8th annual meeting of the Surgical Infection Society of Europe held in Paris, France between 30 May and 1 June 1996.

Intestinal and hepatic oxygen delivery are not improved by catecholamines in endotoxin shock despite increased systemic oxygen delivery

T. Sautner, M. Riegler, C. Wessely, M. Mittlbock, T. Sogukolglu, P. Gotzinger, R. Fugger, *University of Vienna, Austria*

Catecholamine therapy of septic shock aims at haemodynamic stabilization and an increase in systemic oxygen delivery to supranormal values. Systemic oxygen delivery to other organ systems, however, remains unclear. The authors investigated the effects of noradrenaline, adrenaline, and dopexamine on systemic, intestinal and hepatic oxygen delivery in a pig endotoxin shock model.

Pigs weighing 16–20 kg were ventilated with 40 per cent oxygen, with catheters inserted into the vena cava, carotid and pulmonary arteries, and portal vein, with ultrasonographic Doppler flow probes attached (superior mesenteric artery, hepatic artery, portal vein) for measurements of haemodynamic variables and blood sampling. Equilibration for 30 min was followed by 30 min of intravenous infusion of vehicle (controls; $n=3$) or 250 μg *Escherichia coli* endotoxin/kg body-weight. Level of pulmonary capillary wedge pressure was kept constant before and after endotoxin by fluid resuscitation (Ringer solution) alone ($n=3$). In five animals each, mean arterial pressure was additionally increased to 75 per cent of the level before endotoxin administration by noradrenaline or adrenaline. Dopexamine ($n=5$) was administered at the maximum recommended dose of 6 μg/kg/min. Haemodynamic measurements and blood samples were obtained at 30, 90, 150 and 210 min after endotoxin administration. Results are expressed as mean(s.e.m.) and as a percentage of the levels before endotoxin administration.

At 210 min mean(s.e.m.) cardiac index dropped with fluid resuscitation to 35(9) ml/min/kg (30 per cent; $P=0{\cdot}1$). It was increased by noradrenaline to 187(11) ml/min/kg (120 per cent; $P<0{\cdot}001$), by adrenaline to 208(30) ml/min/kg (157 per cent; $P<0{\cdot}001$), and by dopexamine to 513(40) ml/min/kg (135 per cent; $P<0{\cdot}001$) *versus* control of 350(6) ml/min/kg (92 per cent). In spite of this, mean(s.e.m.) intestinal oxygen delivery decreased in all groups over time and was not significantly affected by fluid resuscitation (28·4(6) ml/min; 59 per cent), noradrenaline (32·7(5) ml/min; 65 per cent), adrenaline (12·5(7); 43 per cent) and dopexamine (42·4(12); 80 per cent) *versus* control (35·4(1); 80 per cent; P not significant). Mean(s.e.m.) hepatic oxygen delivery also decreased over time and was not significantly affected by fluid resuscitation (20(22) ml/min; 24 per cent), noradrenaline (33(6); 43 per cent), adrenaline (33(6); 44 per cent) and dopexamine (55(11); 75 per cent) *versus* control (74(1); 62 per cent; P not significant).

After administration of endotoxin, systemic oxygen delivery is increased by noradrenaline, adrenaline and dopexamine, while intestinal or hepatic oxygen delivery cannot be improved.

S-adenosyl-methionine decreases bacterial translocation, and systemic nitric oxide and carbon monoxide production in hepatic ischaemia–reperfusion

J. Arias-Diaz, E. Vara, C. Garcia-Carreras, N. Villa, P. Ortiz, J. L. Balibrea, *Universidad Complutense, Madrid, Spain*

Ischaemia–reperfusion injury of the liver occurs during hepatic surgery, and shock and liver transplantation. Although the specific mechanisms are unclear, it seems that free oxygen radicals play an important role; they can exert cellular damage in a variety of ways, including depletion of glutathione (GSH) and lipid peroxidation. Experimentally-induced decrease of GSH may be prevented by the administration of GSH precursor S-adenosyl-methionine (SaMe) which also seems to play an important role in preserving the structures of cell membranes. This study investigated the possible protective effect of SaMe against the systemic inflammation induced by ischaemia–reperfusion injury of the liver.

Male Wistar rats were separated randomly into three groups. Group 1 underwent a 60-min period of ischaemia of the right lateral lobe, induced by temporary occlusion of the right portal vein and hepatic artery. On restoration of flow to the right lateral lobe, the median and left lateral lobes were excised. Rats in group 2 underwent hepatectomy but without ischaemia–reperfusion, and those in group 3 had sham operation. All animals received intravenous administration of either SaMe 20 mg/kg in 0·5 ml saline, or saline 0·5 ml 15 min before laparotomy. Rats were killed 10 or 120 min after reperfusion and samples of blood (from porta and cava), and liver tissue were taken.

After 120 min of reperfusion, there was a significant increase in liver lipid peroxides (LPO), and in plasma LPO, lipopolysaccharide (LPS), interleukin 6, nitric oxide and carbon monoxide concentrations. SaMe significantly reverted the ischaemia–reperfusion effect on LPO (liver and plasma) and plasma carbon monoxide (mean(s.d.) 66·5(6·3) *versus* 88·9(12·9) nmol/ml, $n=12$, $P<0{\cdot}05$, in cava), and LPS (mean(s.d.) 1·75(0·17) *versus* 2·79(0·18) u/ml, $n=12$, $P<0{\cdot}01$, in cava; and 1·37(0·11) *versus* 2·02(0·17) u/ml, $n=12$, $P<0{\cdot}01$, in porta).

These results suggest a possible beneficial effect of SaMe in liver ischaemia–reperfusion. A decrease in both bacterial translocation and systemic release of nitric oxide and carbon monoxide might contribute to this effect.

Effect of endotoxaemia on L-arginine–nitric oxide pathway in rat pulmonary vascular bed

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Nitric oxide is an endothelial modulator in sepsis and is related to some of the significant complications. The relation of L-arginine–nitric oxide pathway with pulmonary complications in sepsis is not clear. This study determined the alterations in L-arginine–nitric oxide pathway with an endotoxaemia model in rat pulmonary vascular bed.

Endotoxaemia was induced in 26 rats 4 h before the preparation of isolated and perfused lung by intraperitoneal injection of lipopolysaccharide (LPS) 20 mg/kg. Some 28 rats in the control group were given 0·9 per cent NaCl intraperitoneally. After 30 min of perfusion of the isolated lung with Krebs-Henseleit solution (KHS), the effects of various vasoconstrictor or relaxant drugs were studied measuring perfusion pressure via a pressure transducer. Vasoconstriction was achieved with KHS including KCl 15–20 mmol/l and vasorelaxation with acetylcholine 0·02, 0·2 and 20 μg.

The endothelium-dependent vasorelaxation was significantly reduced in the LPS group ($P<0{\cdot}05$). L-Arginine (precursor of nitric oxide) 1 mmol/l, indomethacin (cyclo-oxygenase inhibitor) 10 μmol/l, or dexamethasone (inducible nitric oxide synthase (iNOS) inhibitor) 5 mg/kg pretreatment did not change the acetylcholine-induced endothelium-dependent relaxation in both groups ($P > 0·05$). Indomethacin and L-arginine did not affect this response in either group ($P > 0·05$). L-N-arginine methyl ester and dexamethasone pretreatment increased the vasoconstrictive response to U46619 in the group receiving LPS ($P < 0·05$).

The diminished endothelium-dependent vasorelaxation in the endotoxaemic rat pulmonary vascular bed is probably a result of decreased nitric oxide synthesis from damaged endothelium. Endotoxaemia induces the iNOS in vascular smooth muscle. The increased nitric oxide inhibits the vasoconstrictive response to U46619. This study has demonstrated that indomethacin has no effect on the L-arginine–nitric oxide pathway and L-arginine is not the rate-limiting step in this pathway.

Effect of antibiotics on endotoxin release in patients undergoing critical care

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Recent studies suggest that there is a differential release of endotoxin by different antibiotics, but most were performed *in vitro*. The objective of this study was to evaluate endotoxin release with different antibiotics in patients undergoing critical care. The authors obtained blood samples from critically ill patients before, 60, 120, 180, 240 and 300 min after antibiotic infusion over 3 consecutive days. There were ten patients per antibiotic group (imipenem, cefotaxime, ciprofloxacin, ceftriaxone, tobramycin and vancomycin) with clinical parameters and APACHE (Acute Physiology and Chronic Health Evaluation) II scores included. Endotoxin level and endotoxin neutralizing capacity were determined by a kinetic endotoxin assay with internal standardization (0·5 pg/ml is equivalent to no endotoxin). Interleukin (IL) 6 was measured by a commercially available ELISA (enzyme-linked immunosorbent assay). The mean age of patients was 59 years; age and operation did not influence endotoxin release. Antibiotic administration after 120 and 180 min were the points at which endotoxin release was most likely. Only cefotaxime and imipenem showed a difference in endotoxin release 180 min after antibiotic administration (mean(s.e.m.) cefotaxime at baseline 1·27(1·9) pg/ml, at 180 min 2·2(4·5) pg/ml; Imipenem at baseline 0·5 pg/ml, at 180 min 0·5 pg/ml, $P = 0·08$). IL-6, APACHE II score, temperature and leucocytosis did not differ among the groups.

Conclusions

1. At a certain time after antibiotic administration the likelihood of endotoxin release is increased.
2. There is an increase in endotoxin release after imipenem or cefotaxime administration.
3. IL-6 levels, APACHE II score, temperature, leucocyte levels are not different.
4. Further studies should be performed to investigate endotoxin release in patients undergoing critical care.

Treatment of septic organ failure with gene transfer of an anti-inflammatory cytokine

J. M. Baumhofer, B. Beinhauer, M. A. Rogy, *University Klinik Wien, Austria*

Gene transfer as a new therapeutic modality was evaluated in an experimental model of septic pulmonary organ failure. In an attempt to prevent the deleterious consequences of overwhelming local production of tumour necrosis factor (TNF) α, a gene transfer with the cDNA of the TNF inhibitor p55 and the cDNA of the anti-inflammatory cytokine interleukin (IL) 10 was performed.

Under pentobarbital anaesthesia 35 mg/kg BW, 20 C57/bl mice received an intratracheal instillation of cationic liposomes containing 50 µg of either the pCMV/hp55 or the pcD-SR-α/hIL-10 plasmid. Some 40 h later, the trachea was re-exposed and 10 µg of *Escherichia coli* 0127:B8 LPS in 25 µl of normal saline was instilled. Five hours after the endotoxin challenge, the mice were killed and their lungs removed to be examined for TNF-α content and neutrophil infiltration, as measured by myeloperoxidase levels.

Gene transfer with IL-10, but not with p55, significantly reduced the TNF-α (mean(s.d.) p55 was 500(43) pg/g; mean(s.d.) IL-10 measured 146(58) *versus* controls 382(66)). Similarly, the degree of neutrophil infiltration was reduced by 55 per cent in animals treated with IL-10 but not reduced in those treated with p55 (mean p55 53·2 U/g; mean IL-10 measured 26·4 *versus* controls 58·7).

These results underscore several advantages for the use of gene transfer for septic pulmonary organ failure. First, the specificity of targeting inhibitors to specific organs is greatly increased. Second, the gene transfer schema permits a continued expression of these inhibitors for several days, allowing prolonged delivery of a short-lived antagonist. Finally, local cytokine inhibitors can be directed away from organs where the putative beneficial effects of TNF-α are occuring.

Aminoethylisothiourea, a selective inhibitor of the inducible nitric oxide synthase isoform improves liver circulation and oxygen metabolism in endotoxaemia

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Nitric oxide is an important mediator in sepsis. Treatment with non-selective nitric oxide synthase inhibitors seems to have undesirable circulatory effects. The role of nitric oxide in oxygen metabolism in sepsis and endotoxaemia is only partly known. The authors have studied the effects of the inducible nitric oxide synthase inhibitor aminoethylisothiourea (AE-ITU) on liver perfusion and oxygen metabolism in endotoxaemia.

Nine pigs were given endotoxin 1·7 µg/kg/h as a continuous infusion for 6 h. AE-ITU was given as bolus injection 10 mg/kg after 3 h to seven pigs. Endotoxin caused reductions in mean(s.d.) hepatic artery flow (266(53) *versus* 127(19) ml/min; $P < 0·05$) and mean(s.d.) portal venous flow (663(52) *versus* 323(33) ml/min; $P < 0·05$). Mean(s.d.) hepatic oxygen delivery was reduced from 94(12) to 38(5) ml/min ($P < 0·05$), while hepatic oxygen uptake was almost unchanged as a result of increased oxygen extraction ratio. After AE-ITU injection, liver perfusion increased gradually: mean(s.d.) portal venous flow from 323(33) to 434(26) ml/min and hepatic artery flow from 127(20) to 267(40) ml/min ($P < 0·05$) over 3 h. A rapid increase in extraction ratio was followed by slower increases in hepatic oxygen delivery and uptake: mean(s.d.) hepatic oxygen delivery rose from 38(5) to 60(5) ml/min ($P < 0·05$), mean(s.d.) hepatic oxygen uptake rose from 22(4) to 35(3) ml/min ($P < 0·05$).

The iNOS inhibitor aminoethylisothiourea improves hepatic circulation and oxygen metabolism during endotoxaemia.

Incidence and outcome of enterococcal bacteraemia: a 20-year review from one burn centre

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Intrinsic resistance to cephalosporins and a propensity to acquire other resistance place members of the genus *Enterococcus* among the most antibiotic-resistant of nosocomial pathogens. The recently recognized international spread of glycopeptide (vancomycin) resistant strains and their potential to transfer this resistance evokes further concern.

The authors have investigated the incidence and associated mortality of bacteraemia with enterococci (principally *E. faecalis*) in 4493 consecutively admitted patients with burns.

Enterococci were isolated from the blood of 71 patients (1·6 per cent of admissions, 7·2 per cent of 991 patients with positive blood cultures). Candidaemia occurred more frequently in the cohort with enterococci than the non-enterococci cohort (28 of 71 *versus* 162 of 920; $P<0\cdot001$). The frequency of Gram-negative blood cultures did not differ between enterococci and non-enterococci. Gram-positive cultures other than enterococci were more frequent in the former group (59 of 71 *versus* 651 of 921; $P<0\cdot03$). Comparison of observed mortality with estimates of expected mortality based on burn severity showed that the enterococci cohort was associated with increased mortality in patients with *Candida* sp. or a Gram-negative pathogen isolated from the blood during hospitalization ($P<0\cdot01$). enterococci, either alone or with other Gram-positive bacteraemia (more than 80 per cent staphylococcal), was not associated with added mortality. Infections with vancomycin-resistant organisms were not observed.

Gram-negative or candidal blood infections appear to be significant cofactors associated with increased mortality in patients with enterococci.

Nitric oxide mediates hepatocyte injury

J. H. Wang, H. P. Redmond, D. Bouchier-Hayes, *Beaumont Hospital, Dublin, Ireland*

The degree of acute hepatic failure after severe trauma and sepsis is related to the extent of hepatocyte damage and cell death resulting from either necrosis or apoptosis. The authors have previously demonstrated that tumour necrosis factor (TNF) α and lipopolysaccharide (LPS) can directly lead to hepatocyte necrosis, but not apoptosis. Recent studies have shown that reactive oxygen intermediates (ROIs) and nitric oxide are capable of inducing apoptosis in eukaryotic cells. However, it is unclear whether ROIs or nitric oxide are involved in hepatocyte cell death.

This study evaluated the role of nitric oxide and ROIs in hepatocyte cell death (apoptosis *versus* necrosis). Hepatocytes were isolated from Sprague-Dawley rats, and cultured with the nitric oxide donor, sodium nitroprusside or the ROI generation system, hypoxanthine-xanthine oxidase (HX–XOD) and H_2O_2. The effects of LPS, TNF-α and interferon γ alone or in combination with different antioxidants and the nitric oxide synthase inhibitor, N-methyl-arginine (NMA) on hepatocytes were also assessed.

	Medium	SNP 0·5 mmol/l	TNF-α 25 ng/ml
Apoptosis (%)	2·8(0·7)	16·0(3·9)*	2·3(1·0)
AST (U/ml)	9·8(2·1)	26·0(4·8)*	30·0(3·7)*
LDH (U/ml)	501(42)	698(70)*	871(56)*
Necrosis (%)	0·0(0)	8·6(2·8)*	11·0(2·6)*
NO (μM)	2·7(0·8)	12·0(2·9)*	4·2(1·3)
	+ SOD 400 U/ml	+ SOD 400 U/ml + NMA 0·5 mmol/l	
Apoptosis (%)	13·0(4·3)†	4·3(1·8)‡	
AST (U/ml)	22·0(4·1)†	15·0(3·5)‡	
LDH (U/ml)	757(60)†	653(55)‡	
Necrosis (%)	7·8(1·9)†	4·3(1·7)‡	
NO (μM)	8·4(2·2)†		

Values are mean(s.d.); *$P<0\cdot05$ *versus* medium, †$P<0\cdot05$ *versus* tumour necrosis factor (TNF) α only, ‡$P<0\cdot05$ *versus* TNF-α + superoxide dismutase (SOD). SNP, sodium nitroprusside; NMA, N-methyl-arginine; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; NO, nitric oxide

Sodium nitroprusside (0·0625–4·0 mmol/l) caused a dose-dependent increase in hepatocyte apoptosis as confirmed by flow cytometry and DNA gel electrophoresis. ROIs generated by HX–XOD and H_2O_2 did not induce hepatocyte apoptosis, but were responsible for hepatocyte necrosis. TNF-α alone failed to induce hepatocyte apoptosis, but when combined with superoxide dismutase resulted in increased hepatocyte nitric oxide production and apoptosis. This effect was attenuated by NMA. Sodium nitroprusside also induced hepatocyte damage as represented by hepatocellular enzyme aspartate aminotransferase and lactate dehydrogenase release and hepatocyte necrosis. Moreover, TNF-α mediated hepatocyte damage and necrosis could be further reduced by the combination of antioxidants and NMA.

These results indicate that ROIs preferentially induce hepatocyte necrosis, but not apoptosis. Induction of nitric oxide resulted in both hepatocyte apoptosis as well as necrosis, which suggests that overproduction of nitric oxide may be detrimental during the systemic inflammatory response syndrome.

Induction of the inflammatory response after cardiopulmonary bypass and the effect of immunoglobulin prophylaxis

C. H. Fischer, B. Baumann, R. E. Silber, R. G. Holzheimer, *Chirurgie Universitätsklinik Wurzburg, Germany*

Patients undergoing cardiopulmonary bypass (CPB) develop a postsurgical inflammatory response. Endotoxin and cytokines have been implicated in multiple organ failure and may contribute to the immunocompromised state seen after bypass. The authors have previously described the effects of immunoglobulin (Ig) prophylaxis in patients undergoing CPB on chemotactic neutrophil migration. This study evaluated the effect of immunoglobulin M enriched immunoglobulin (pentaglobin) on tumour necrosis factor (TNF) α, interleukin (IL) 6, IL-8, IL-10 and TNF-α R1 in peripheral plasma and on postoperative infections.

There were three study groups: group 1 received pentaglobin and perioperative antibiotics ($n=20$); group 2 received perioperative antibiotics ($n=20$); and group 3 received antibiotics before and during operation ($n=10$). Ig prophylaxis was started 20 h before operation. Cytokines were measured by ELISA (enzyme-linked immunosorbent assay).

Intraoperative complications occurred in one patient (perioperative myocardial infarction); there were eight postoperative infective complications. There were 40 men and 10 women with a mean age of 62 years. In group 1 mean(s.e.m.) IL-6 levels increased from baseline (7·7(1·5) pg/ml) at 60 min of CPB (96·2(14·4) pg/ml) ($P<0\cdot01$). There was no difference between patients treated with Ig and group 2 (baseline: 5·9(0·9) pg/ml; 60 min CPB: 117·2(26·1) pg/ml). The IL-6 levels in groups 1 and 3 were 96·2(14·4) pg/ml and 143(27·3) pg/ml ($P=0\cdot08$). TNF-α levels were similar in all groups. TNF-R1 levels decreased significantly from baseline level to the start of CPB in all groups and increased significantly to levels above baseline 60 min after CPB ($P<0\cdot01$). TNF-R1 level was lower in group 1 than group 3 at 60 min but this was not significant. IL-8 levels increased from baseline to 60 min after CPB; there was no difference between groups. IL-10 levels increased significantly from baseline to 120 min after CPB ($P<0\cdot01$); there was a significant difference between group 1 and 3 at 120 min after CPB ($P<0\cdot05$).

CPB is accompanied by increased cytokine production in peripheral plasma. There is no difference between patients treated with Ig and those with perioperative antibiotic treatment. However, patients who received antibiotics before operation had decreased IL-10, and increased IL-6 and TNF-R1 levels.

Cyclosporin A antagonizes liver tumour necrosis factor α and nitric oxide production in a rat model of intestinal ischaemia–reperfusion

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Loss of intestinal barrier function has been implicated in the development of systemic infection and septic shock. The liver seems to be a primary target organ for lipopolysaccharide (LPS)-induced systemic inflammation. Polymorphonuclear phagocytes (PMN) play an important role in mediating ischaemia–reperfusion-induced injury. As cyclosporin A (CsA) inhibits the activity of PMN and macrophages, the authors designed the study to investigate whether CsA prevents the release of several inflammatory mediators in a rat model of intestinal ischaemia–reperfusion.

Male Wistar rats were assigned randomly to four groups. Rats in group 1 underwent a 60-min period of ischaemia by clamping the superior mesenteric artery. Group 2 received identical treatment, except that CsA 0·5 mg/kg intravenous in 0·5 ml saline was administered. Groups 3 (saline) and 4 (CsA) underwent sham operation. Some 60 min after reperfusion, samples of plasma (from porta, infrahepatic cava and suprahepatic cava), liver and small bowel were taken. In survival experiments, rats were followed until death.

CsA decreased mortality rate ($n = 30$, 23 *versus* 60 per cent; $P < 0{\cdot}01$) and blocked ischaemia–reperfusion induced increase in LPS levels in porta (mean(s.e.m.) 0·38(0·15) *versus* 0·99(0·07) U/ml, $n = 5$, $P < 0{\cdot}05$), and infrahepatic cava ($n = 5$, 0·27(0·03) *versus* 0·69(0·17) U/ml; $P < 0{\cdot}05$). CsA also decreased.

Ischaemia–reperfusion induced increases in plasma lipid peroxides and carbon monoxide. In liver tissue, CsA prevented the ischaemia–reperfusion-induced increase in tumour necrosis factor (TNF) α, phospholipase A_2 and cGMP concentrations. Nitric oxide plasma levels after ischaemia–reperfusion were significantly increased in cava, more markedly in suprahepatic ($n = 5$, 257·3(42·7) *versus* 47·1(11·7) nmol/ml; $P < 0{\cdot}01$) than in infrahepatic ($n = 5$, 94·6(12·5) *versus* 47·9(3·2) nmol/ml; $P < 0{\cdot}01$), but were not modified in porta.

These results suggest a possible protective effect for CsA in intestinal ischaemia–reperfusion. This effect could be mediated in part by a reduction in the release of inflammatory mediators from the liver.

The gut as a cytokine-producing organ: relationship to bacterial translocation

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The convincing pathological role for bacterial translocation in the development of multiple organ failure (MOF) in animal studies has not been confirmed in humans. One explanation for this controversy may be the property of gut immune cells to release cytokines even in the absence of detectable bacterial translocation.

Wistar rats were bled to 30 mmHg for 30 min. After reperfusion, 4 and 24 h later mononuclear cells of the small bowel were separated and incubated for 48 h with lipopolysaccharide (LPS) 250 ng/ml (S. friedenau). Tumour necrosis factor (TNF) α (WEHI 164) and interleukin (IL) 6 (B 13·29) concentrations were measured in supernatants of shock and sham operated rats ($n = 6$ per group). Two other groups ($n = 6$) were fed after shock for 5 days with enteral or parenteral nutrition. In all animals mesenteric lymph nodes (MLNs) were harvested and the number of viable bacteria was calculated.

Maximal LPS-induced cytokine production for TNFα and IL-6 was observed after reperfusion. In contrast to IL-6 release priming of intestinal mononuclear cells was suppressed for TNFα with a significant hyporesponsiveness after 24 h ($P < 0{\cdot}05$ *versus* sham). This was reversed after 5 days of feeding with significantly higher TNFα and IL-6 concentrations in enterally fed animals ($P < 0{\cdot}05$). Bacterial translocation to MLN could not be detected during the first 24 h after reperfusion. In four of six rats fed parenterally bacteria could be recovered (2626 CFU/g tissue) in MLNs on day 5 compared with none of the rats fed enterally.

Cytokine release from the gut may predispose to organ failure in the early stage of shock and is differently regulated for TNFα and IL-6. Cytokine production may be induced by translocating intestinal bacteria which do not reach the MLNs. In this model bacterial translocation is only related to parenteral nutrition indicating that translocation to MLN may be a secondary phenomenon.

Inflammatory cytokines and matrix metalloproteinases 2 and 9 profiles in healing wounds

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Wound fluid and plasma was collected from 25 patients after simple mastectomy for primary breast cancer (age range 32–82 years), and ten patients after left-sided colonic resection for primary colorectal cancer (age range 62–80 years). Wound fluid was obtained at intervals following surgery, via sterile drainage systems inserted at surgery and simultaneous venesection was performed at each time point. Samples were centrifuged to remove cellular debris and stored in aliquots at − 80 °C until use.

Inflammatory cytokines interleukin (IL) 1β, IL-6, IL-8, tumour necrosis factor (TNF) α, interferon (IFN) γ were assayed in fluid and plasma using standard ELISA (enzyme-linked immunosorbent assay) techniques and matrix metalloproteinases (MMPs) 2 and 9 in fluid and serum by electrophoresis on gelatin substrate. Cytokine assays were run in duplicate against known standards and detection sensitivity and specificity confirmed by spiking with standard. MMP activity was confirmed by eliminating activity with EDTA and phenanthroline; serine and cysteine protease inhibitors had no effect.

For all cytokines except IL-1β, (for which the concentrations remained at or below the level of detection), there exists a significant difference between concentrations in wound fluid and in plasma at all time points ($P < 0{\cdot}001$). IFN-γ concentration peaks in wound fluid by 6 h after surgery; IL-6 at 24 h; IL-8 at 48 h and TNF-α at 72 h. Similarly, for MMP-2 and MMP-9 a significant difference exists between fluid and serum levels ($P < 0{\cdot}001$). MMP-2 rises slowly to peak at 72 h, before gradually declining towards baseline levels, while MMP-9 rises rapidly to peak at 24 h, before declining. Wound infection is associated with raised and persistently raised cytokine and MMP concentrations antedating the onset of clinical wound infection by 24 h.

There exists a definite pattern of inflammatory mediation in uncomplicated wound healing. The disturbance of mediator profile seen in aberrant wound healing antedates the onset of clinical signs and could be considered as a predictive marker for delayed wound healing.

Role of the network of inflammatory mediators in the pathologicalmechanism of post-traumatic infections

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This study determined the role of the network of inflammatory mediators (tumour necrosis factor (TNF) α, interleukin (IL) 6, nitric oxide (NO) and eicosanoids) in the pathologicalmechanism of infections following trauma.

Twenty patients with severe trauma (Injury Severity Score between 22 and 57) were included in this study. TNFα, IL-6, IL-2 sR, 6-ketoPGF$_1$ thromboxane (TX) B_2 and leukotriene (LT) B_4 were measured in plasma samples taken on days 1, 3, 7 and 10 after trauma. Spontaneous and endotoxin stimulated production of TNFα, IL-6, IL-2sR, IL-1, NO$_2$/NO$_3$ as well as prostaglandin (PG) E$_2$, 6-keto pgF$_{1}\alpha$, TXB$_2$ and LTB$_4$ by peripheral blood mononuclear cells (PBMCs) were assessed on the same days after trauma as plasma measurements.

The infection rate was 54 per cent. Infections occurred between days 5 and 8 after trauma. Infected patients demonstrated a significantly lower level of plasma TNFα from day 1 to day 7 than non-infected patients. Spontaneous and endotoxin-stimulated production of TNFα by PBMCs was also significantly lower in infected patients during the study period. Spontaneous and endotoxin stimulated productions of IL-6 and pgE$_2$ were markedly higher in infected patients. Spontaneous and endotoxin stimulated NO$_2$/NO$_3$ production by PBMCs was significantly lower in infected patients on days 1 and 3, while as a result of infection NO production increased from day 7 to day 10. No significant changes were observed in the other mediators studied.

These findings suggest a negative feedback mechanism between TNFα and IL-6 as well as pgE$_2$. Furthermore the low production of TNFα and NO (important mediators of microbial killing) may be responsible for infection following severe trauma.

Taurine attenuates nitric oxide and reactive oxygen intermediate-dependent hepatocyte injury

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Hepatocyte cell death predisposes to liver failure during the systemic inflammatory response syndrome (SIRS). The authors have found that nitric oxide (NO) and reactive oxygen intermediates (ROIs) are involved in hepatocyte cell death. Taurine has cytoprotective properties through its actions as an antioxidant and has been shown to protect human endothelial cells against apoptosis. The authors hypothesized that taurine may protect against hepatocyte cell death.

This study evaluated the role of taurine in the prevention of hepatocyte apoptosis and necrosis mediated by NO and ROIs. Hepatocytes were isolated from Sprague-Dawley rats and cultured with lipopolysaccharide (LPS) 0·1 μg/ml alone, and in combination with either antioxidants (DMSO 0·5 per cent; SOD 400 U/ml; NAC 7·5 mmol/l; GSH 7·5 mmol/l) or taurine 0·5 mg/ml for 24 h. Hepatocyte apoptosis was determined by percentage of hepatocytes with hypodiploid DNA as assessed by flow cytometry and DNA gel electrophoresis. Hepatocyte necrosis was assessed using a ^{51}Cr release assay. NO was measured by determination of nitrite/nitrate concentration.

LPS in the presence of antioxidants led to hepatocyte apoptosis, while LPS alone failed to induce hepatocyte apoptosis. Taurine significantly attenuated LPS plus antioxidant-mediated hepatocyte apoptosis, and this correlated with taurine-mediated NO inhibition. Taurine also significantly reduced LPS-mediated hepatocellular enzyme release and hepatocyte necrosis. However, taurine did not prevent sodium nitroprusside (SNP 0·5 mmol/l; NO donor)-mediated hepatocyte apoptosis (mean(s.e.m.) 14(4·2) *versus* 16(3·9) per cent) and necrosis (mean(s.e.m.) 7·9(2·3) *versus* 8·6(2·8) per cent) indicating that NO inhibition occurs at the level of inducible NO synthase (iNOS) mRNA expression.

These results demonstrate that taurine attenuates hepatocyte apoptosis through iNOS inhibition and hepatocyte necrosis through inhibition of both NO and ROI and indicate a prophylactic and therapeutic role for this amino acid during SIRS.

Matrix metalloproteinase-9 may be an early marker of disturbances in postoperative wound healing

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The predominant cellular responses in early primary healing of surgical wounds are from infiltrating neutrophils and macrophages, basement membrane remodelling by capillary endothelia, and proliferation and migration of epithelial cells, all of which involve pericellular proteolysis largely as a result of production and secretion of matrix metalloproteinase (MMP) 9.

MMP-9 was assayed in the wound fluids and sera of nine patients 0–96 h after mastectomy, and in nine patients 24–120 h after abdominal surgery, and quantified by scanning gelatin substrate electrophoresis gels within their linear response range. The protease was confirmed as MMP by eliminating activity using ethylenediamine tetra-acetic acid and phenanthroline; serine and cysteine protease inhibitors had no effect. The MMP was shown to have a gelatin-binding site by differential affinity for gelatin and casein. The assay itself demonstrated the MMP to degrade gelatin and have an apparent molecular weight of 90 kDa and shift to lower molecular weight forms after preactivation with aminophenyl mercuric acetate.

In both acute patient groups MMP-9 levels peaked at 24 h, a fourfold increase from baseline levels for the group who underwent mastectomy (group 1), and tenfold for the group who had abdominal surgery (group 2). A clear drop was seen after 24 h in both groups and was significant between 24 and 48 h (group 1, $P = 0{\cdot}01$; group 2, $P = 0{\cdot}001$). In fluid collected from a mastectomy wound subsequently found to be infected, there was no drop in MMP-9 levels between 24 and 48 h, and at 72 h further elevation was seen. Similarly, in chronic non-healing wounds, high MMP-9 levels are maintained over long periods, as the wound is unable to progress beyond the early stages of healing. In all groups, the serum levels of MMP-9 approximated to baseline levels found in acute wound fluids.

Wounds that are healing express fluid levels of MMP-9 which peak at 24 h, and show a clear decrease between 48 and 72 h. MMP-9 in postoperative wound fluid provides a marker of delayed healing which may be evaluated non-invasively within 48 h of closure.

Surgical trauma does not decrease the resistance against infection

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Surgical trauma alters immune response. Cell-mediated reactions are depressed, antibody production is increased or decreased depending on the type of antigen used, total phagocytic activity is transiently reduced and remote inflammatory reactions are inhibited. It is not known whether these alterations have an influence on the resistance against infection. Therefore, the authors studied the effects of two different surgical procedures on survival after induction of *Escherichia coli* or *Staphylococcus aureus* peritonitis.

White Wistar R/A rats weighing 200–500 g were either anaesthetized alone (controls), underwent a hind limb amputation, or had a left lumbar incision with posterior opening of the peritoneal cavity. One, 7 or 14 days later peritonitis was induced by implantation in the subhepatic space of a sponge soaked either with 2×10^8 *E. coli* colony-forming units (c.f.u.) or 2×10^8 staphylococci c.f.u. Each group consisted of between 27 and 30 animals. Survival rates were recorded for 7 days.

After induction of *E. coli* peritonitis, survival rates were the highest in the two groups of rats submitted to a lumbar intraperitoneal approach 1 or 7 days earlier (97 and 100 per cent respectively at 7 days) when compared with rats undergoing amputation (80 and 87 per cent) or controls anaesthetized at the same times (60 and 70 per cent). The difference in controls was only significant for the lumbar incision groups ($P < 0{\cdot}005$). There was no difference between controls and animals operated on 14 days earlier. Similar results were obtained with staphylococcal peritonitis.

Although surgical trauma depresses various aspects of the immune response, it does not decrease the resistance against monomicrobial intraperitoneal infections. On the contrary, previous procedures opening the abdomen improve rat survival in this peritonitis model.

Clinical significance of endotoxin release in elective colorectal operations following single-shot antibiotic prophylaxis

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In this hospital all patients undergoing bowel surgery receive standard perioperative antibiotic prophylaxis with a second generation cephalosporin and metronidazole. *In-vitro* and animal studies have shown a correlation between the severity of endotoxin release and certain antibiotics. Few *in vivo* studies, in patients with sepsis, have highlighted the role different antibiotics may have in endotoxin release. The authors investigated the effects of single-shot antibiotic prophylaxis during and after elective colorectal operations on endotoxin release.

Thirteen patients with rectal carcinoma were enrolled. Exclusion criteria of the study group were the discovery of liver metastases either before or during operation, previous treatment with antibiotics, and liver dysfunction. Cefotaxime 2 g was given to five patients and cefotiam 2 g in combination with 500 mg metronidazole to eight patients at the start of anaesthesia.

The endotoxin base level of all patients was 0·7 pg/ml. A significant rise to 16·1 pg/ml was detected 15 min after antibiotics were given intravenously. There was still a significant rise in endotoxin after 2 h. At the end of the perioperative period endotoxin decreased to 5·4 pg/ml. Between 1 and 3 days after operation endotoxin decreased continuously to baseline level. After treatment with cefotaxime the endotoxin level increased 15 min after the infusion to 1·7 pg/ml and 2 h later a peak of 1·9 pg/ml was measured, while the combination of cefotiam and metronidazole caused a rise to a maximum of 25·1 pg/ml. Endotoxin neutralizing capacity declined continuously to a minimum on day 1 after operation and returned to the baseline apparent before surgery on the third postoperative day. No patient showed an increase in heart rate, temperature or change in blood pressure. No patient had infection during follow-up.

The authors demonstrated a significant increase in endotoxin 15 min after antibiotic administration. Endotoxin release may be caused by antibiotics rather than the surgical procedure. Cefotaxime caused lower endotoxin release. Measurement of endotoxin neutralizing capacity in plasma did not reveal any significant difference. No clinical relevance of endotoxin release was observed during elective uncomplicated colorectal operations; this might not be true for patients undergoing critical care or those with sepsis.

Smoking increases the incidence of surgical wound infections and duration of hospitalization

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Wound infections are common complications of surgery. Cigarette smoking has acute and chronic systemic effects that decrease tissue perfusion and oxygen delivery and has long been suspected of impairing wound healing. However, the effects of smoking on the incidence of postsurgical wound infections remain unclear.

The authors studied prospectively 180 patients with a physical status of American Society of Anesthesiologists grades I, II and III undergoing elective colonic surgery. All patients were given a third-generation cephalosporin for three days after surgery. Postoperative surgical pain was treated using patient-controlled analgesia. An independent observer evaluated surgical wounds on a daily basis until discharge. Any observed pus was cultured; the combination of pus and a positive culture identified infected wounds. The date of hospital discharge was determined by the attending surgeon.

Morphometric characteristics, anaesthetic management and infection risk scores were similar in smokers and non-smokers. There were 15 of 55 culture-positive surgical wound infections in smoking patients (27 per cent) and 8 of 125 in those who did not smoke (6 per cent) ($P<0{\cdot}001$). Furthermore, the mean(s.d.) duration of hospitalization was significantly longer in the smokers (14(4) *versus* 12(4) days, $P=0{\cdot}002$).

Smoking increased the incidence of surgical wound infections fourfold, suggesting that aggressive wound surveillance after operation might be helpful in smokers. Smoking markedly decreases tissue oxygen delivery and the resulting low partial pressures persist for hours after each cigarette. Prolonged postoperative administration of supplemental oxygen may be helpful in smokers.

Therapy for fungaemia improves neutrophil-derived oxygen radical production in multiple organ failure

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Neutrophil (PMN)-derived long-lived oxygen radicals such as hypochlorous acid (HOCl) are potent bactericidal and fungicidal agents. PMN-HOCl causes phenotypic switching of *Candida albicans* colonies to a form that is more susceptible to killing by PMN. PMN from patients with multiple organ failure (MOF) have a depressed ability to inhibit *C. albicans*. We determined the rate of production of PMN-HOCl in a series of patients with *C. albicans* fungaemia before and after institution of antifungal therapy.

Eleven patients with MOF were recruited; four had culture-positive *C. albicans* fungaemia (age range 58–72 years; group 1) and seven acted as controls (age range 54-75 years; group 2). PMNs were obtained using a discontinuous two-step centrifugation on Ficoll-Hypaque density gradients; HOCl production was determined by the taurine chlorination method. All assays were performed in triplicate.

The maximum PMN-HOCl production rate for group 1 was 0·242 (median 0·2065) nmol/million PMN/min before treatment and 0·791 (median 0·5825) nmol/million PMN/min after treatment ($P<0{\cdot}01$). The PMN-HOCl rate curves for group 1 after treatment and for group 2 were similar.

These findings suggest that antifungal therapy improves the production of long-lived oxygen radicals by the PMN in MOF complicated by *C. albicans* fungaemia and may help explain the decrease in mortality due to antifungal therapy in this group of patients.

Immunological monitoring of *Escherichia coli* sepsis induced multiple organ failure during a time course model on LEW.1W rats

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This study evaluated the benefit of endotoxin, interferon (IFN) γ, tumour necrosis factor (TNF) α, biopterin (BH_4), phospholipase (PL) A_2 and isocitrate-dehydrogenase (ICDH) for early detection and monitoring of multiple organ failure (MOF) caused by Gram-negative sepsis.

LEW.1W rats underwent thiopental anaesthesia and an intraperitoneal injection of 6 ml *Escherichia coli* (K1H)/haemoglobin solution. Control animals received physiological saline solution 6 ml intraperitoneally. All animals receiving *E. coli* developed Gram-negative sepsis. After 30 min a significant bacteraemia was found ($z=350$ organisms/ml; $P<0{\cdot}01$) which increased up to 6 h ($z=52500$ organisms/ml; $P<0{\cdot}0005$). Increased endotoxinaemia was measured after 3 h ($z=8{\cdot}35$ EU/ml; $P<0{\cdot}05$) with a maximum after 6 h ($z=27{\cdot}86$ EU/ml,

$r=1571$; $P<0\cdot01$). No correlation between bacteraemia and endotoxinaemia was found. Serum PLA$_2$ activities were raised after 2 h ($z=153\cdot5$ U/l, $r=180$; $P<0\cdot01$) with higher activities up to 6 h ($z=139\cdot8$ U/l, $r=165\cdot9$; $P<0\cdot005$). The synthesis of BH$_4$ was increased continuously to 6 h (not significant). ICDH was increased after 3 h ($z=1\cdot82$ mU/l; $P<0\cdot05$) and a maximum after 6 h ($z=3\cdot5$ mU/ml; $P<0\cdot01$). After 6 h, IFN-γ showed maximum concentrations in most of the rats with sepsis ($z=357\cdot33$ pg/ml, $r=12\,669$). TNF-α expression was highest in the second hour ($z=0\cdot78$ pg/ml, $r=5\cdot65$) and in the sixth hour ($z=1\cdot81$ pg/ml, $r=8\cdot27$). Positive correlations between endotoxinaemia and IFN-γ in the fourth hour ($r_s=0\cdot67$; $P<0\cdot05$) and sixth hour ($r_s=0\cdot58$; $P<0\cdot05$) were found. IFN-γ expression correlated with the TNF-α concentrations at 2 h ($r_s=0\cdot79$; $P<0\cdot01$) and 6 h ($r_s=0\cdot85$; $P<0\cdot001$). The course of *E. coli* sepsis was characterized by a permanent drop in thrombocyte counts after the first hour ($P<0\cdot01$) to the prefinal phase of MOF ($P<0\cdot0005$).

In patients with acute *E. coli* sepsis, serological variables could be useful for an early diagnosis of sepsis.

Biological response modifiers increase monocyte antigen presenting capacity via upregulation of HLA-DR and intercellular adhesion molecule (ICAM) 1 without affecting lymphocyte CD18 or ICAM-1 expression

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The ability of monocytes to maintain, restore, or increase their antigen presentation capacity correlates with the outcome in badly injured patients. Immunomodulation targeting monocyte antigen presentation might therefore represent an important tool in fighting surgical infections. It has been postulated that intercellular adhesion molecule (ICAM) 1 on monocytes binding to lymphocyte CD18, the receptor for ICAM-1, can enhance antigen presentation.

This study determined if muramyl dipeptide (MDP), a small bacterial cell wall component with immunomodulatory properties, and lipopolysaccharide (LPS) can modulate human leucocyte antigen (HLA)-DR and ICAM-1 expression on human monocytes and affect ICAM-1 and CD18 expression on lymphocytes.

Whole blood was obtained from three healthy volunteers and incubated for 1, 3, 6, 12, 18 and 24 h at 37°C with 0·9 per cent saline, LPS 0·1 μg/ml or MDP 1 μg/ml. Flow cytometry with monoclonal anti-HLA-DR, anti-CD18, and anti-ICAM-1 was used to determine the mean fluorescent intensity of monocytes and lymphocytes expressing HLA-DR, ICAM-1 and CD18.

With both LPS and MDP treatment, ICAM-1 expression on monocytes showed a continuous increase up to 24 h, whereas HLA-DR-expression peaked (twofold increase compared with baseline) at 6 and 12 h. Although LPS and MDP had similar significant effects, LPS showed an enhanced ICAM-1 expression (twofold at 12 h and threefold at 24 h) when compared with MDP. Neither lymphocyte CD18 nor ICAM-1 expression changed over time.

MPD and LPS upregulate both HLA-DR and ICAM-1 expression on monocytes *in vitro*. The simultaneous increase in ICAM-1 expression on monocytes may stabilize HLA-DR-dependent antigen presentation via CD18 on lymphocytes. These data indicate that the enhancement of antigen presentation after MDP or LPS is a result of monocyte rather than lymphocyte upregulation.

Clinical outcome of patients undergoing major abdominal operation and fed enterally shortly after surgery

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Supplementation of enteral formulas with immunonutrients improves host immune response and decreases the incidence of postoperative septic complications in surgical and critically ill patients. This study evaluated the effect of early postoperative administration of an enriched enteral diet in 126 patients undergoing major abdominal surgery for gastric or pancreatic cancer.

The patients were randomized after operation into three groups to receive: (1) standard enteral formula ($n=43$); (2) the same formula enriched with arginine, RNA and omega-3 fatty acids ($n=40$); (3) isonitrogenous, isocaloric total parenteral nutrition (TPN) ($n=43$). Jejunal infusion was started within 12 h after surgery. Infusion rates were progressively increased reaching the full regimen (25 kcal/kg, 0·25 g nitrogen/kg) on day 4 after operation. Clinical assessments were: timing of bowel movements, rate of intolerance and interruption of the enteral feeding, incidence and severity of postoperative infections, and length of hospital stay after surgery.

The groups were comparable for age, type of operation, rate of malnutrition and blood transfusion, duration of surgery, intraoperative blood loss and preoperative hospital stay. The rate of intolerance to enteral feeding was 22 per cent (18 of 83). Of the 18 patients with gastrointestinal discomfort, five (28 per cent) needed a temporary interruption and reduction of the infusion velocity. The patients fed enterally, regardless of formula, showed a quicker bowel passage of gas and stool (mean(s.e.m.) 2·9(0·7) and 5·7(1·1) days respectively) than the TPN group (mean(s.e.m.) 3·8(1·1) and 7·0(1·2) days respectively) ($P<0\cdot05$). The overall infectious complication rate was 18 per cent (22 of 126). In the group receiving the arginine-enriched formula the rate of sepsis was 12·5 per cent (five of 40) *versus* 19 per cent in the standard enteral formula, and in the TPN group (eight of 43) ($P=0\cdot18$). The severity of septic complications (based on sepsis score) was mean(s.e.m.) 3·2(0·5) in the arginine-enriched group *versus* 6·6(2·1) in the standard group and 8·0(2·2) in the TPN group ($P<0\cdot05$). Mean(s.d.) length of postoperative stay was 12·8(2·2) days in the group receiving arginine-enriched formula *versus* 16·5(3·0) in the standard group, and 16·2(3·3) in the TPN group ($P<0\cdot05$).

Early postoperative enteral nutritional support, after major abdominal surgery, is feasible, well tolerated and allows a quicker recovery of gut function.

Relation between the anatomical site of intestinal disruption and infective morbidity in abdominal trauma

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The anatomical site of intestinal disruption in abdominal trauma determines the bacterial inoculum released into the peritoneal cavity, and may influence the infective complication rate. The results of gastrointestinal disruption at various anatomical segments of the alimentary tract were analysed, in a trauma centre dealing with large numbers of abdominal injuries.

During a 2-year period 712 patients, 598 men and 114 women with a median age of 26 years, underwent operation for abdominal trauma and were found to have either solid or no visceral injury (group 1, $n=384$) or isolated hollow visceral injury: stomach or small bowel (group 2, $n=176$) or right or left colon (group 3, $n=152$). There were 432 stab wounds (mean Injury Severity Score (ISS) 30·4, mean Abdominal Trauma Index (ATI) 21), 141 gunshot wounds (ISS 31·2, ATI 28·3) and 139 blunt trauma (ISS 30·7, ATI 17·8). Infective complications were described as regional (peritoneal cavity and surgical or traumatic access routes) or distant, and mortality as early (48 h) or late, related or not-related to sepsis.

The overall mortality rate was 9·7 per cent (69 of 712) and the late mortality rate was 3·9 per cent (group 1, 3·9 per cent; group 2, 3·6 per cent; group 3, 5·1 per cent). Regional infective complications occurred more in group 3, 41 per cent than in group 2, 21 per cent and group 1, 9 per cent (group 3 *versus* group 2; $P<0\cdot05$; group 3 *versus* group 1; $P<0\cdot01$). Complication rate correlated with the ATI score. Distant septic complications were also more frequent in group 3, 19 per cent than in group 2, 6 per cent and group 1, 9 per cent (group 3 *versus* group 2; $P<0{\cdot}05$). Left colon injuries fared worse than right colon, and colon worse than small bowel. Stomach perforations were often associated with chest trauma. ISS and ATI were important determinants of outcome, in addition to mechanism of injury and delay between injury and operation. Splenectomy did not influence the results either way.

Conclusions

Hollow visceral injury is associated with more complications than solid visceral injury, and the infection pattern of injury to the gastrointestinal tract is variable. The more distal the alimentary tract disruption, the higher the septic complication rate.

Colonic injury: is primary repair really safe? Analysis in critically ill patients

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As primary repair of colonic injuries gains wider acceptance, the authors performed this study to assess its safety in a compromised subgroup of patients.

A descriptive prospective study over an 11-month period of all patients admitted with colonic injury to the surgical intensive care unit (SICU) was undertaken. Revised Trauma Score, Injury Severity Score and Acute Physiology and Chronic Health Evaluation II were assessed. Intraoperative shock, soiling and use of inotropic support were documented. Events were recorded until discharge from the SICU or patient's death.

Some 58 patients were analysed: 38 survived and 20 died. Both groups had comparable demographics. Soiling, shock and inotrope use was more prevalent in the non-survivor group. Technique of colonic repair in the group of patients who survived was as follows: direct closure ($n=26$), resection ($n=9$) and primary anastomoses and primary colostomy ($n=3$). In the group of non-survivors the techniques were: direct closure ($n=15$), resection and anastomoses ($n=8$), and colostomy ($n=1$). Breakdown of repair occurred in one patient in each group, both direct closure.

Primary repair of colonic injury in the critically ill seems safe. The mortality is related to the magnitude of physiological derangement and not to the method of repair. Emphasis should lie in rapid and efficient trauma care.

Perioperative hypothermia increases the incidence of surgical wound infection and prolongs duration of hospitalization

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Wound infections are common complications of surgery. Core hypothermia decreases subcutaneous oxygen tension, impairs immune function and reduces resistance to experimental skin infections. The authors tested the hypothesis that core hypothermia increases both the incidence of surgical wound infections and the duration of hospitalization.

A total of 200 patients (American Society of Anesthesiologists grades I, II and III) undergoing elective colonic surgery were studied. They were randomly assigned to normal thermal management ($n=96$, hypothermic group) or additional warming ($n=104$, normothermic group) using a Bair Hugger forced-air heater. All patients were given a third-generation cephalosporin at incision and for three days after operation. An observer strictly blinded to group assignment and core temperatures evaluated the wounds on a daily basis until discharge and at clinic visits for a total of 30 days: wounds with culture-positive pus were considered infected. The time of suture removal and the date of discharge was determined by the blinded attending surgeon.

Morphometric characteristic and anaesthetic management were similar in the two groups. Mean(s.d.) core temperatures at the end of surgery in the hypothermic group were significantly less than those in the warmed patients (34·5(0·4) *versus* 37·0(0·4) °C). Hypothermia tripled the incidence of wound infections and markedly increased time to suture removal ($P<0{\cdot}01$) and duration of hospitalization ($P<0{\cdot}04$).

These data indicate that hypothermia is an important factor predisposing to wound infection. Furthermore, delayed suture removal suggests that wound healing was also impaired. Maintaining intraoperative normothermia is thus likely to decrease infective complications and reduce length of hospitalization.

Postoperative infection complications after biliary stone surgery: a European study

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This is a prospective, controlled study in seven European countries: Spain, Turkery, Germany, Norway, Hungary, Italy and Switzerland. The study took place between 1 February and 30 April 1995, and included patients aged 18 years or over with gallstones undergoing surgical treatment.

A total of 280 surgical patients was included. Mean age was 54·8 years; 27·5 per cent were men and 72·5 per cent women. Some 78·9 per cent of the patients were classified as having clean-contaminated surgery, 13·9 per cent contaminated and 3·6 per cent dirty surgery. In 80 per cent the surgical procedure was performed by staff members; 85 per cent received antibiotic prophylaxis.

Twenty-one patients developed septic complications after operation (7·5 per cent) of which 12 (4·3 per cent) were wound infections; one patient (4·8 per cent) had an intra-abdominal infection. In clean-contaminated surgery, the rate of overall postoperative infections was 5·9 per cent, 7·7 per cent in contaminated and 50 per cent in dirty ($P<0{\cdot}001$). The wound infection rate was 3·2 per cent in clean-contaminated surgery, 7·7 per cent in contaminated and 20 per cent in dirty ($P<0{\cdot}02$). In laparoscopic cholecystectomy the overall rate of postoperative infections was 3·6 per cent *versus* 12·6 per cent in open cholecystectomy ($P<0{\cdot}01$); 2·4 per cent and 6·3 per cent wound infection respectively. Mean age of the patients who developed postoperative septic complications was 61·5 years and 54·2 years for those who did not ($P<0{\cdot}03$). Duration of the postoperative period was 5 days in patients without infection and 13 days in patients with infection ($P<0{\cdot}0001$). The micro-organism most frequently isolated in postoperative infections was *Escherichia coli*. Two patients died (0·7 per cent), one of them from a septic cause (0·4 per cent).

This prospective study carried out in seven European countries using the computer programme "Surgery" has helped to establish the rate of postoperative infections after biliary stone surgery in Europe.

Non-invasive perioperative monitoring of the volume of distribution of narrow therapeutic range antibiotics during surgical prophylaxis

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Antimicrobial prophylaxis for colorectal surgery demands mechanical bowel decontamination and oral non-absorbable antibiotics. Frequently parenteral peroperative antibiotics are used, either as monotherapy or as combined prophylaxis.

This study analysed the impact of whole gut lavage fluid compartments and, in consequence, on several pharmacokinetic parameters of 'narrow therapeutic range antibiotics' used as prophylaxis in colorectal surgery.

The changes on extracellular water (ECW) and total body water (TBW) induced by whole gut lavage were measured using whole body bioelectrical impedance analysis (BIA) in a group of 15 patients undergoing colorectal surgery. Another group of five patients undergoing major abdominal surgery without intestinal lavage was used as control. Distribution volume was determined by pharmacokinetics analysis using gentamicin as a compartmental probe.

Baseline TBW and ECW before whole gut lavage were similar in both groups (control group: TBW 34·55(11·98), ECW 16·51(3·74) l; lavage group: TBW 35·59(6·5), ECW 15·99(2·82) l). However, at the end of the bowel preparation, the lavage group showed a decrease in TBW, particularly in ECW (TBW 34·30(6·54), ECW 14·95(2·82) l) which indicates a volume loss of 1·29(2·28) and 1·03(1·51) l for TBW and EWC respectively. Also, this decrease affects the distribution volume of gentamicin which was contracted in the lavage group (0·19(0·05) l/kg) and therefore, serum gentamicin concentrations were higher (1·60(0·55) μg/ml). In the control group these values were 0·34(0·14) l/kg and 1·25(0·24) μg/ml respectively.

Pharmacokinetics parameters for hydrophilic drugs with high extravascular distribution and narrow therapeutic range, as gentamicin, are modified by gut lavage used for mechanical intestinal decontamination, and such changes may be monitored before operation by BIA.

Patients referred after failed operations for severe acute pancreatitis: results of repeat operation and prolonged active drainage

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Various surgical techniques have been proposed in the management of infected necrosis complicating acute pancreatitis but no consensus has been reached. Recent series still report a mortality of between 25 and 50 per cent. The authors analysed the impact of prolonged active drainage in a group of patients with infected necrosis, who were referred after surgery had failed.

Between 1979 and 1994, 196 patients with severe acute pancreatitis were treated surgically, 71 per cent being referred from other centres. Sixty-four patients had been operated on in the primary unit and were deteriorating in spite of surgical drainage. The patients were referred after failed surgery for severe acute pancreatitis between 1979 and 1994. Isolated complications of surgery for acute pancreatitis (fistula, bowel stenosis, pseudocyst, biliary problems, nutritional problems) were excluded. Only patients with continuing extensive tissue necrosis in the pancreatic or peripancreatic sites were included. The main indications for surgery were ongoing sepsis (72 per cent), enterocutaneous fistula (14 per cent) and haemorrhage (14 per cent). All patients had extensive necrosis of the pancreatic and peripancreatic tissue. Infection of the necrosis could be demonstrated in 84 per cent of patients. Perforation of a hollow viscus was found in 30 per cent. All patients were operated on within 2 days of admission. The necrotic tissue was debrided and the sites of necrosis packed with Mikulicz capillary drains. After 12 days, these drains were replaced by spiral drains for continuous irrigation. A daily high-pressure lavage was undertaken, allowing removal of solid debris of necrotic tissue. A Witzel jejunostomy was made to provide continuous enteral nutrition during the long postoperative period of intensive care, and a loop ileostomy was raised to protect the colon from necrosis and fistulation.

Twelve patients (19 per cent) died, mainly from sepsis and multiple organ failure. The postoperative course was complicated in a majority of patients, the main adverse events being gastrointestinal tract fistulas (22 per cent), pancreatic external fistulas (12 per cent), and haemorrhage (16 per cent). Overall, 28 per cent of patients required repeat operation. Mean duration of hospital stay in the group of survivors was 65 days. The two main current trends in the surgical treatment of infected pancreatic necrosis are open drainage or closed cavity lavage. The authors propose a technique combining the advantages of both and yielding satisfactory results in terms of mortality.

Severe sepsis in a cardiothoracic intensive care unit

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The authors prospectively studied 2615 patients of mean(s.d.) age 60·8(8·7) years, admitted consecutively to the cardiothoracic intensive care unit (ICU) after open-heart surgery. Patients were included in the protocol if they had clinical signs of sepsis and pathogen isolated in blood culture(s).

Severe sepsis developed in 41 patients who underwent cardiac surgery (1·5 per cent). There were 30 men and 11 women of mean(s.d.) age 64·7(9·5) years. These patients underwent coronary artery bypass graft surgery ($n = 19$), valve replacement surgery ($n = 8$), combined surgery ($n = 7$) or other surgery ($n = 7$). The patients had a prolonged mean(s.d.) bypass time of 149(59) min and aortic cross clamp time of 88(42) min compared with the control group ($P = 0{\cdot}001$). They received more blood tranfusions (mean(s.d.)16·2(10·6) blood units and 21·3(9·4) plasma units) and more inotropic agents (mean(s.d.) 2·6(0·9)) compared with the control group ($P = 0{\cdot}001$). Major complications in the operating room involved 19 patients. The majority of them ($n = 40$) presented major complications in the ICU. Twelve patients underwent repeat operation for bleeding, while 16 patients were reintubated because of severe hypoxaemia. Fifty-four episodes of sepsis were recorded. Microbial isolates were *Staphylococcus epidermidis* ($n = 26$), *Staphylococcus aureus* (MSSA) ($n = 5$), *Enterococcus* sp. ($n = 5$), *Streptococcus faecalis* ($n = 1$), *Candida albicans* ($n = 11$) and Gram-negative bacteria ($n = 6$). The majority of microbial pathogens were isolated during the first 2 weeks in the ICU, but the majority of candida was usually isolated during the postoperative day. The patients with sepsis had prolonged mean(s.d.) ventilatory support (31·4(21·3) days), prolonged ICU stay (40·1(24·7)days) and hospital stay (47·7(27·1)days). Mortality rate was 31·7 per cent. Acute Physiology and Chronic Health Evaluation II scoring system was similar for both surviving and non-surviving patients with sepsis (mean 20·2).

Patients with sepsis had significantly higher bypass time and aortic cross-clamp time compared with the control group ($P < 0{\cdot}0001$) and received more blood transfusions and inotropic agents perioperatively compared with the control group ($P < 0{\cdot}0001$). The group of patients who developed sepsis in the ICU underwent more repeat operations and reintubations compared with the control group ($P < 0{\cdot}0001$). Sepsis of microbial origin developed during the first 2 weeks and sepsis due to *Candida* sp. had usually developed by day 20 after surgery. Patients with sepsis had significantly prolonged mechanical ventilatory support, ICU and hospital stay compared with the control group ($P < 0{\cdot}0001$) and mortality rate was high (31·7 per cent).

Granulocyte macrophage-colony stimulating factor in the treatment of experimental peritonitis

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Immune dysfunction is a constant defect in patients with severe sepsis and contributes to mortality. The activity of granulocyte macrophage-colony stimulating factor (GM-CSF) was investigated in order to detect a possible reduction in mortality and its mechanism.

Peritonitis was induced by caecal ligation and puncture (CLP) in Sprague Dawley rats weighing 250 g. Rats were divided into three groups: group 1 underwent CLP only; group 2 received CLP plus antibiotics (tobramycin 3 μg/g/day and clindamycin 40 μg/g/day); and group 3 had CLP plus antibiotics plus GM-CSF 1 ng/g/day. CR3 membrane expression before and after stimulation with formyl-methionyl-leucyl-phenylalanine 10^{-7} mol/l was measured by flow cytometry and expressed as mean fluorescence intensity (MFI) in order to determine polymorphonuclear neutrophil activity. Sampling was performed before (T0), 24 (T1) and 48 (T2) h after CLP.

The mortality rate was 75 per cent in group 1 and 60 per cent in group 2 (P not significant). Treatment with GM-CSF (group 3) reduced mortality to 23 per cent ($P<0{\cdot}05$). We detected a 53 per cent increase in CR3 expression after stimulation at T0. The improvement was reduced to 17·8 per cent at T1 and 93 per cent at T2. Antibiotic treatment did not affect CR3 expression, while GM-CSF partially restored the response: 29 per cent at T1 and 35 per cent at T2 ($P<0{\cdot}05$).

GM-CSF was able to significantly decrease the mortality rate of peritonitis induced by CLP in rats. This result is associated with a restored capacity of neutrophil response to a secondary stimulus which is depressed in patients with sepsis.

Peritoneal cytokine response: *in vitro* study on interleukin (IL) 1β and IL-6 release in two different models

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Mainstays of operative management of intra-abdominal infections are elimination of the focus, peritoneal toilet to reduce bacterial contamination and prevention of recurrent infection. We investigated the early influence of taurolidine, iodine and saline solution on secretion of interleukin (IL) 1β and IL-6 by human peritoneal mesothelial cells (HPMCs) as well as by cultured human peritoneum.

HMPCs grown up to monolayer, and peritoneum, taken from the cut edges of the parietal peritoneum during intestinal resection, were incubated with taurolidine 1 per cent, iodine 2 per cent, saline solution 0·9 per cent and as control with Ham's F12 medium with and without lipopolysaccharide (LPS) 10 μg/ml. After 1 h, 3 h and 6 h IL-1β and IL-6 concentrations were measured in supernatants by enzyme-linked immunosorbent assay.

HMPC showed a 2·4- to 3·5-fold increase in IL-6 levels between 1 and 3 h after incubation with Ham's F12 medium with and without LPS, or with saline. This response was depressed by taurolidine. In peritoneal cultures IL-6 levels increased to 2000 pg/ml after incubation with LPS, taurolidine, saline and control medium within 1 h. In cultured human peritoneum IL-1β values uniformly increased under the influence of LPS, saline solution and control medium without LPS suggesting that irrigation fluids were able to induce secretion of the pro-inflammatory cytokine. Again, this response was depressed by taurolidine. In contrast, after instillation of all solutions in HMPCs only very low levels of IL-1β were found. With the exception of an early increase in IL-1β in HMPC cultures, in both models only low IL-6 and IL-1β levels were found after treatment with iodine. Control studies with standard IL-6 and IL-1β concentrations, however, suggest that iodine influences commercially available enzyme-linked immunosorbent assay resulting in false-negative values.

Irrigation alone leads to a significant release in IL-6 in both models, and IL-1β levels showed a minor increase in the supernatants of cultured peritoneum and was almost undetectable in mesothelial monolayers. Endotoxin did not seem to influence the response of mesothelial cells, but may be responsible for a detectable increase in IL-1β levels in macrophage-containing peritoneal tissue cultures. All these responses were depressed or even blocked by the addition of taurolidine to the irrigation fluid.

Phagocytic and chemotactic function of neutrophils in peritonitis

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Polymorphonuclear neutrophil (PMN)) function is an essential component of the host defence against infection. However, infection itself may alter PMN activity. The authors evaluated phagocytosis and chemotaxis in control and infected blood PMN.

Control blood PMNs were obtained from 25 healthy volunteers. Infected blood and peritoneal PMNs were obtained from 50 patients with peritonitis undergoing laparotomy. Blood samples from patients were drawn before operation, and on days 1, 5 and 8 after operation. Neutrophils were obtained by gradient density separation using Ficoll-Hypaque. Chemotactic activity was measured by agarose plate method and phagocytosis was measured as the intracellular uptake of complement opsonized yeast particles.

Phagocytosis and chemotaxis were both significantly reduced in peritonitis patients compared with controls ($P<0{\cdot}001$). The reduction in function was significantly more marked and persisted for a longer duration in patients who developed complications compared with those who had uncomplicated recovery ($P<0{\cdot}01$). Blood and peritoneal PMN activity was similar in all patients.

In conclusion: (1) blood and peritoneal PMNs show a similar response to infection; (2) presence of serious infection suppresses the functions of PMNs; (3) PMN activity can predict morbidity.

Inhibitory effect of human peritoneal exudate on bacterial growth

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Gram-positive and Gram-negative micro-organisms are sensitive to the antibacterial action of biological fluids such as serum, amniotic fluid, or pleural exudate. The authors have evaluated the antibacterial activity of postoperative peritoneal exudates from patients with and without peritonitis.

Serum and exudate samples were tested at different concentrations against *Escherichia coli* ATCC 10789, *Proteus* sp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Antibacterial activity was detected by a continuous-recording turbidimetric method and expressed as delay in the beginning of the exponential growth curve of bacterial cultures.

Postoperative exudates showed activity against *E. coli* and proteus but not against pseudomonas and klebsiella. This activity was time and concentration dependent and differed from the respective serum activity. With regard to antibiotic therapy (cefotiam) the minimum inhibitory concentration in the serum paralleled those in the exudates and both inhibited the growth of *E. coli*, proteus and *Staphylococcus aureus*, but not klebsiella.

From these preliminary results it is concluded that there is a time dependent antibacterial activity against certain bacterial species in postoperative peritoneal exudates. Antibodies, the peroxidase antimicrobial system, complement and Schlievert's glycoprotein may explain this effect. The interaction of this activity with antibiotic treatment and its influence on outcome variables remains to become established.

Drainage of the lower abdomen in severe postoperative peritonitis: experience with the Mikulicz capillary drain in 255 consecutive patients in intensive care unit

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Johannes von Mikulicz designed and used a large gauze packing occupying the whole pelvic space coming out through the midline incision to drain fluids by capillary suction and evaporation. Mikulicz's device was preferred to other methods such as conventional tube drainage, open abdomen plus scheduled relaparotomy. The authors report experience with the Mikulicz capillary drain (MCD) in patients with severe postoperative peritonitis.

All patients managed between 1980 and 1994 for postoperative peritonitis and requiring MCD as a mode of drainage of the pelvis were included. Patients with localized abscesses or limited contamination treated without MCD were excluded. The origin of the peritonitis was the upper gastrointestinal tract in 48 patients and the lower tract in 207. There were 170 men and 85 women with mean age 52 years; 165 (65 per cent) patients were referred from other centres. The peritonitis was diffuse in 223 patients while 32 had an abscess in the pelvis. At the end of the operation, a large parachute-shaped gauze was placed in the pelvis, down to the pouch of Douglas and filled with gauze swabs, thus forming a large cylinder coming out of the abdomen through the inferior end of the midline incision. The MCD was left in an open appliance and removed between days 12 and 14 after operation.

Hospital mortality rate was 24·3 per cent (62 of 255). Intra-abdominal abscesses recurred in 21 (8 per cent) patients and early reoperation rate was 21 per cent (53 of 255). There was no bowel fistula as a result of the MCD. Among the survivors, 109 patients underwent restoration of bowel continuity at a mean period of 63 days after first operation. Few adhesions were encountered and a good restoration of the peritoneal surface was observed. Mortality rate after this stage was 0·9 per cent (1 of 109).

The MCD appears to be efficient for the drainage of the lower abdomen, both for the pouch of Douglas and interloop spaces. Its uncomely appearance, its main inconvenience, may be improved by daily cleaning with oxygenated water, thus allowing its more aesthetic use.

Lipopolysaccharide, tumour necrosis factor (TNF) and TNF receptor levels in systemic and portal blood in patients during laparotomy

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The presence of lipopolysaccharide (LPS) has been documented in the portal blood of patients undergoing laparotomy, and it is believed that LPS could be responsible for developing shock in some of these patients, an observation which is controversial. The authors have measured LPS, tumour necrosis factor (TNF) and soluble TNF receptors (TNFR55 and TNFR75) levels in 30 patients (neoplasia, 15; intra-abdominal infections, three; aortoiliac revascularizations, five; hepatic grafts, two; biliary tract reconstructions, two; and inflammatory bowel disease, three). Portal (P) and systemic (S) blood were taken at the start (P1) and at the end (P2, S2) of laparotomy (mean time: 1·5 h). TNF and soluble TNF receptors were measured by enzyme-linked immunosorbent assay and LPS by the lymphocyte amoebocyte lysate assay, and compared with values measured in normal blood donors.

	TNF pg/ml	TNFR55 pg/ml	TNFR75 pg/ml	LPS pg/ml
P1	39·7(23·2)*	2·4(1·7)*	4·3(3·2)*	14·8(13·6)*
P2	23·3(21·6)*	2·7(1·8)*	4·9(3·4)*	13·1(7·0)*
S2	26·6(24·2)*	2·6(1·8)*	4·8(3·8)*	n.a.
Controls	4·0(3·0)	1·1(0·7)	2·4(1·4)	5·7(3·1)

Values are mean(s.d.). n.a., Not available. *$P < 0·05$ *versus* controls

TNF, soluble TNF receptor and LPS levels were higher in patients than in controls. The highest values were found in patients with intra-abdominal infections and in those undergoing hepatic transplantation. These values were similar in portal and systemic blood. Mean levels of LPS were not different before or after laparotomy. No patient developed shock.

The presence of increased TNF, TNF receptor and LPS levels indicated activation of the host. In contrast, laparotomy did not induce any further LPS translocation from the gut, nor any resulting monocyte activation as measured by TNF production or shedding of TNF receptors.

Effect of pneumoperitoneum on the extent and severity of peritonitis induced by gastric ulcer perforation in rats

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Laparoscopic surgical management of perforated gastroduodenal ulcer is technically feasible. Whether a pneumoperitoneum influences the extent or severity of peritonitis induced by peptic ulcer perforation remains unclear.

In rats, gastric ulceration induced by gastric instillation of 50 per cent ethanol 2 ml was followed by standardized gastrotomy to simulate gastric ulcer perforation. Animals were randomly assigned to four groups undergoing pneumoperitoneum and four control groups. In the groups undergoing pneumoperitoneum, CO_2 was insufflated intraperitoneally 6, 9, 12 and 24 h after gastrotomy to a pressure of 4 mmHg for 60 min. In controls the peritoneal cavity was punctured without gas insufflation. All animals were killed 5 h after pneumoperitoneum or abdominal puncture alone. Blood samples and intra-abdominal swabs were cultured for bacteria. Based on the histological specimen taken from peritoneum, liver, left kidney, spleen and first jejunal loop, a peritonitis severity score (PSS) was estimated.

No significant differences between the groups undergoing pneumoperitoneum and control groups were observed 6 and 9 h after gastrotomy. Twelve hours after gastrotomy, cultures of blood samples and abdominal swabs were positive in 67 and 75 per cent, and mean(s.d.) PSS was 20·8(2·2) in the pneumoperitoneum group compared with 42 per cent ($P < 0·05$), 42 per cent ($P < 0·05$) and 11·3(1·5) ($P < 0·01$) in the control group, respectively. Cultures of blood samples and abdominal swabs taken 24 h after gastrotomy were positive in 83 and 100 per cent, and mean(s.d.) PSS was 22·1(1·5) in the group who underwent pneumoperitoneum compared with 42 per cent ($P < 0·05$), 50 per cent ($P < 0·01$), and 11·8(2·4) ($P < 0·01$) in the control group.

These results indicate that in rats, pneumoperitoneum aggravates the extent and severity of peritonitis, when the interval between gastric ulcer perforation and pneumoperitoneum lasts 12 h or more.

The following abstracts were presented as posters

Do free gallstones in the peritoneal cavity increase morbidity?

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Perforation of the gall bladder with spillage of stones and/or bile, with or without bacteria, into the peritoneal cavity occurs frequently during laparoscopic cholecystectomy, and stones are left in the peritoneal cavity. This study evaluated the effect of retained stones and related factors on further complications.

A total of 135 Swiss Albino mice were divided into four groups and the effects of stones, bile and bacteria were studied. The study groups were: group 1 (15 mice), control, group 2 (30); laparotomy and intraperitoneal 0·1 ml 4×10^6 *Escherichia coli*; group 3 (30), laparotomy + intraperitoneal sterile gallstones; group 4 (30), laparotomy + intraperitoneal sterile gallstones + intraperitoneal 0·1 ml 4×10^6 *E. coli* + intraperitoneal 0·1 ml sterile bile. One-third of the animals in each group were killed at the end of 1, 2 and 4 weeks. The animals were explored for intraperitoneal abscess formation, adhesion, perforation, fistula or obstruction. Microbiological cultures were obtained from abscesses, peritoneum and blood.

There was no mortality. Adhesions were found in all groups: three of 15 mice, six of 30, 23 of 30, 19 of 30 and 20 of 30 in groups 1, 2, 3, 4 and 5 respectively. No abscess formation was found in groups 1, 2 or 3 but abscess was present in seven mice in group 4 and six of group 5. There was one intestinal obstruction due to adhesions secondary to gallstones in group 4. In the laparotomy–gallstone–*E. coli* group abscess formation increased ($P<0\cdot0001$), while addition of bile did not have any effect. Gallstones increased the rate of adhesion formation ($P<0\cdot0001$), while *E. coli* and/or bile did not increase the risk ($P=0\cdot75$). Gallstones in the peritoneal cavity increased this risk tenfold (95 per cent confidence interval 4·22–24·53).

The presence of free gallstones in the peritoneal cavity with *E. coli* and/or sterile bile leads to an increase in abscess and adhesion formation. With these results retrieval of intraperitoneal stones during laparoscopic cholecystectomy is advisable particularly in acute cholecystitis.

Clinical features of septic encephalopathy in surgical and trauma patients in the intensive care unit

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Encephalopathy and/or polyneuropathy occurs in 70 per cent of patients with severe sepsis. Possible mechanisms of neurological dysfunction are: microabscess formation, blood-brain barrier and brain metabolism alterations, neurotransmitter disorders, reduced cerebral blood flow or cerebral perfusion pressure (CPP), acute liver and/or renal failure. We have analysed the incidence, clinical features and outcome of septic encephalopathy in surgical and trauma patients and evaluated the possible derangements of cerebral haemodynamic and metabolic variables, in a selected group of subjects with combined traumatic and septic encephalopathy.

Over a 3-year period a total of 37 patients with severe sepsis were observed in this intensive care unit (ICU). In 29 patients without head injury (group 1) all signs of neurological dysfunction as well as metabolic alterations were recorded. Comatose patients underwent cerebral computed tomography (CT) and electroencephalography (EEG). In the subpopulation of eight head-injured patients (group 2) cerebral haemodynamic and metabolic variables were studied, based on the monitoring of intracranial pressure (ICP), CPP, and cerebral extraction of O_2 (CEO_2). CEO_2 was calculated as the arteriojugular difference in oxyhaemoglobin saturation; neurological status was evaluated by Glasgow Coma Scale (GCS).

In group 1, 24 (82·7 per cent) patients presented with signs of encephalopathy represented by: obtundation (27·6 per cent), confusion or agitation (38 per cent), coma (20·7 per cent), and seizures (13·8 per cent). Diffuse EEG abnormalities were recorded. No cerebral CT alterations were observed. Only in few cases encephalopathy might be due to liver and/or renal dysfunction. In group 2, the complications included: GCS score impairment (75 per cent), CPP decrease (100 per cent), late ICP rise (75 per cent), enhanced CEO_2 (62·5 per cent).

Encephalopathy frequently occurs in severely septic ICU patients and requires aggressive treatment of sepsis. It can reverse after successful surgical and/or medical treatment of infection, but in patients with brain injury the cerebral derangements may be life-threatening and can worsen the neurological outcome. The results obtained in group 2 indicate that the multivariate approach to cerebral haemodynamic and metabolic variables is clinically relevant in close evaluation and management of combined traumatic and septic encephalopathy.

Effect of L-arginine concentration and nitric oxide synthase inhibition on human neutrophil chemotaxis

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Nitric oxide is synthesized from the amino acid L-arginine by the enzyme nitric oxide synthase (NOS). These experiments examine the effect of varying L-arginine concentration and NOS inhibition on human neutrophil chemotaxis.

Neutrophils from ten normal subjects were suspended in varying concentrations of L-arginine (0, 400, 800, 1200 μmol l^{-1}) and allowed to migrate through Boyden chemotaxis chambers for 30 min. This was repeated with and without NOS inhibition by ^{G}N-monomethyl-L-arginine (LNMMA) and D-arginine at L-arginine concentrations of 0 and 800 μmol l^{-1}. The number of neutrophils migrating through to the distal side of each filter was then determined microscopically.

There was a significant dose related reduction in neutrophil chemotaxis with increasing concentration of L-arginine. NOS inhibition resulted in a significant increase in neutrophil chemotaxis ($P<0\cdot003$ for LNMMA, $P<0\cdot025$ for D-arginine; − L-arg/ + LNMMA *versus* + L-arg/ − LNMMA, $P<0\cdot001$; − L-arg/ + LNMMA *versus* − L-arg/ − LNMMA, $P<0\cdot01$; − L-arg/ + D-arg *versus* + L-arg/ − D-arg, $P<0\cdot05$; − L-arg/ + D-arg *versus* − L-arg/ − D-arg, $P<0\cdot05$).

These results provide evidence that the NOS pathway may exert some control over the basal chemotactic abilities of human neutrophils, in that dose related increases in its substrate results in progressive reduction of chemotaxis, whereas blockade of this pathway enhances neutrophil migration.

Downregulation of macrophage lipopolysaccharide-induced nitric oxide synthase messenger RNA expression by an immunomodulator

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Inducible nitric oxide synthase (iNOS) has been implicated in the pathophysiology of sepsis. The role of iNOS in sepsis is complex and may be either detrimental or beneficial depending upon a variety of factors, such as levels and time course. The authors have reported that immunoprophylaxis with (1-3)-β-D-glucan phosphate will ameliorate septic sequelae in patients with trauma. In this study the effect of glucan phosphate on iNOS messenger RNA (mRNA) expression in a murine macrophage cell line was examined.

J774A.1 cells (2×10^6 per well) were pretreated with glucan phosphate over a dose range of 1–500 μg ml^{-1} for 60 min before challenge with lipopolysaccharide (LPS) 1 μg ml^{-1} (*Escherichia coli* 055:B5) for 4 h. Media, glucan phosphate or LPS alone served as controls. As additional controls, glucan phosphate and LPS were added simultaneously or the order in which the reagents were added was reversed (i.e. LPS before glucan phosphate). The iNOS mRNA expression was assessed by Northern blot hybridization with a [^{32}P]2′-deoxycytidine 5′ triphosphate-labelled iNOS complementary DNA probe. Autoradiograms were digitized by scanning densitometry and quantified by computer assisted image analysis.

Glucan phosphate, as a single regimen, did not induce iNOS mRNA expression. LPS, as a single regimen, markedly enhanced iNOS mRNA expression in J774A.1 cells at 4 h. Pretreatment of LPS-challenged J774A.1 cells with glucan phosphate resulted in a 25 per cent (1 μg ml^{-1}) and 60 per cent (10–500 μg ml^{-1}) reduction in iNOS mRNA expression. Likewise, the simultaneous administration of glucan phosphate and LPS resulted in a 60 per cent reduction in iNOS mRNA expression.

These data indicate that glucan phosphate will downregulate macrophage LPS-induced iNOS mRNA expression.

Ability of hepatocyte supernatants to increase the production of inflammatory cytokines by monocytes

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The increased production of interleukin (IL) 6 after trauma or sepsis causes an increase in acute-phase protein synthesis by hepatocytes. This study determined whether supernatants from IL-6-stimulated hepatocytes could increase the production of tumour necrosis factor (TNF) and IL-6 by lipopolysaccharide (LPS)-stimulated monocytes.

Hep G cells (5×10^5 per ml) were cultured in the presence of IL-6 100 units ml^{-1} for 1 and 7 days. Human monocytes were cultured for 24 h with 50, 100 or 200 μl of the supernatants plus LPS 4 $\mu g\ ml^{-1}$.

Monocytes stimulated with LPS in the presence of 50, 100 or 200 μl hepatocyte supernatant (1-day culture) produced mean(s.d.) 16(1), 28(2) or 32(0·5) units ml^{-1} TNF respectively. Monocytes stimulated with LPS in the presence of 50, 100 or 200 μl hepatocyte supernatant (1-day culture) produced mean(s.d.) 635(14), 941(37), 1009(40) units ml^{-1} IL-6. The production of both cytokines was significantly greater in the presence of 200 μl compared with 100 μl or 50 μl hepatocyte supernatant. Results were similar for 7-day cultures.

Supernatants from IL-6-stimulated hepatocytes can act synergistically with LPS to increase the production of inflammatory cytokines by monocytes. This could lead to perpetuation of the inflammatory response after trauma and sepsis.

Bacteria and location in necrotizing fasciitis

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Necrotizing fasciitis (NF) is a life-threatening soft tissue infection. The re-emergence of group A streptococcal (GAS) infections and associations to NF are observed.

Patients with NF were consecutively treated by a standardized procedure. After admission, material was obtained by sterile puncture of bullae and by taking aerobic and anaerobic blood cultures. At operation debrided tissue and aspirated fluid was transferred in aerobic and anaerobic cultures. A standardized aggressive surgical therapy was supported by intensive care and administration of piperacillin and tazobactam.

Twenty-five patients (11 men, 14 women of mean(s.d.) age 59·7(12·3) years) were treated. Six patients died. The infection was community acquired ($n = 19$) or of nosocomial origin ($n = 6$). Sixteen infections were localized on the extremities. Six solely GAS infections and ten mixed aerobic infections occurred in this group. All nine patients with abdominal or anogenital NF had mixed infections of aerobic and anaerobic bacteria. Frequently isolated bacteria were *Staphylococcus aureus* (ten), *Streptococcus pyogenes* (eight), *Escherichia coli* (eight) and *Bacteroides fragilis* (nine).

In NF, mixed infections are found. GAS infections are localized to the extremities. Anaerobic bacteria are found in cases of anogenital NF. The support of surgical intervention by appropriate antibiotics has to include the probable broad spectrum of bacteria.

Inflammation and adhesion molecules

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Adhesion molecules play an important role in inflammation. One of the selectins, P-selectin, is the first to be expressed in leucocyte–endothelial cell interactions, and it is therefore possible that blocking P-selectin will change the inflammatory response after ischaemia. The authors used the immunoglobulin (Ig) G murine monoclonal antibody PB1·3 in a 90-min total hepatic ischaemic model.

A total of 150 male Sprague–Dawley rats (250–275 g) were distributed into six groups: normal, sham, ischaemic control, PB1·3 30 min before reperfusion, PB1·3 at reperfusion and PB1·3 5 min after reperfusion. Survival, liver function, histology, and levels of myeloperoxidase, tumour necrosis factor, interleukin 1, superoxide dismutase, catalase, glutathione peroxidase and superoxide anion were assessed.

There was an increase in survival from 15 to 55 per cent, improvement in liver function and histology, less neutrophil infiltration and less free radical production, which were statistically significant.

P-selectin plays an important role in inflammation, behaving as a key in the unchaining of other processes.

Effect of serum derived from patients with sepsis on healthy donor monocytes parallels decreased cytokine release from monocytes from patients with sepsis

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Potential therapeutic strategies in the treatment of sepsis are direct manipulation of cells and neutralization of dysregulatory agents in the serum. In order to define monitoring parameters for therapy, the authors investigated monocyte function in patients with sepsis and the effect of their serum on healthy donor monocytes.

Tumour necrosis factor (TNF) α and interleukin (IL) 10 release in whole blood after stimulation with LPS 1·0 $\mu g\ ml^{-1}$ was measured 2–5 days after onset of clinical symptoms in patients with sepsis with haemodynamic instability requiring catecholamines and dysfunction of at least two organs. In parallel, the serum of blood samples from healthy donors was substituted by serum from the patients with sepsis, resulting in a whole blood assay with healthy donor cells in a septic environment.

In septic cells, proinflammatory TNF release was decreased compared with that in healthy controls (mean(s.d.) 135(84) *versus* 2408(240) pg ml^{-1}, $P = 0·02$). Anti-inflammatory IL-10 release was also decreased (mean(s.d.) 1447(479) *versus* 11 458(3237) pg ml^{-1}, $P = 0·06$). Serum from patients with sepsis decreased TNF release (mean(s.d.) 2057(157) *versus* 1086(195) pg ml^{-1}, $P = 0·02$) and IL-10 release (mean(s.d.) 15 312(6278) *versus* 7554(2688) pg ml^{-1}, $P = 0·13$) in healthy donor cells.

Monitoring cell function in parallel with serum effects on cell regulation may provide a chance to evaluate the effect of new therapeutic tools in the treatment of sepsis.

Hypertriglyceridaemia induced by intralipid does not alter the tumour necrosis factor response to lipopolysaccharide

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Previous studies indicate that administration of triglyceride (TG)-rich lipoproteins suppresses the plasma tumour necrosis factor (TNF) response, and reduces mortality to intravenous bacterial lipopolysaccharide (LPS) challenge. Because intralipid treatment has also been suggested to reduce LPS-induced death, the present study was initiated to determine whether this artificial lipid emulsion would impair the plasma TNF responses to LPS.

Two experimental protocols were used. In series 1, rats received a primed constant infusion of vehicle (245 mmol l^{-1} glycerol in saline) or 10 per cent intralipid (1 ml; 2 ml h^{-1}) starting 2 h before low- or high-dose LPS infusion (17 or 170 $\mu g\ h^{-1}\ kg^{-1}$ respectively), and continuing throughout the 4-h post-LPS observation period. In series 2, rats were injected intravenously with galactosamine 375 mg kg^{-1} followed immediately by LPS 15 $\mu g\ kg^{-1}$. Animals in series 2a received 3 ml vehicle or intralipid 1 min after LPS. For series 2b, LPS was mixed with vehicle or intralipid 15 min before injection of the respective mixture.

In series 1, mean(s.d.) plasma TG concentrations were 76(6) and 620(99) mg dl^{-1} in the vehicle and intralipid infused rats respectively, just before LPS challenge. Some 5 min after intralipid injection in series 2, plasma TG was greater than 700 mg dl^{-1} and had declined to mean(s.d.) 102(22) mg dl^{-1} by 2 h after injection. Intralipid-induced hypertriglyceridaemia failed to alter the plasma TNF response which generally peaked 90 min after initiating LPS challenge ($P > 0{\cdot}05$). In addition, intralipid treatment did not alter the temporal TNF response to LPS challenge. In series 1, the TNF response to low-dose LPS was less than the response to high-dose LPS ($P > 0{\cdot}05$).

These results suggest that hypertriglyceridaemia produced by intralipid administration does not impair the ability of LPS to elicit macrophage production and release of TNF. Thus, parenteral feeding with this artificial emulsion does not impair this important macrophage host defence response.

Management of the abdominal wall in diffuse postoperative peritonitis: primary closure using an absorbable mesh

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Closure of the abdominal wall in postoperative peritonitis may be difficult. The abdomen may have to be left open or through-and-through retention sutures used, both risking iatrogenic fistula. The authors avoid leaving the abdomen open and use either conventional closure or skin closure with relaxation incisions. To enhance the protection of bowel, a polyglactin mesh is added.

A total of 157 patients were treated between 1982 and 1994 and represented 40 per cent of all patients with diffuse peritonitis after operation. Placement of a polyglactin mesh was deemed necessary by the operating surgeon when fascial necrosis and/or excessive tension suggested a high risk of postoperative dehiscence. Ninety-nine per cent of the patients were referred from other centres, including 32 per cent referred after failure of one or several operations to control postoperative sepsis. The origin of the sepsis was upper gastrointestinal tract in 49 patients (31 per cent), small bowel in 56 (36 per cent), appendix in ten (6 per cent) and colon in 42 (27 per cent). The peritonitis was diffuse in 135 patients and localized in 22. The mean number of severity factors was 2·87. All patients were managed with complete debridement of the peritoneal surface, elimination of the contaminating source and capillary drainage. The mesh was laid on the bowel loops without fixation. The abdominal wall was closed over the mesh using two different methods: fascial and cutaneous layers in 36 patients (23 per cent), cutaneous layer and relaxation incisions in 121 (77 per cent).

The overall mortality rate was 48 of 157 (31 per cent). Twenty patients (13 per cent) had a recurrent intra-abdominal abscess. Twelve patients had parietal complications: partial dehiscence (six), complete dehiscence (four) or suppuration (two). A small bowel fistula occurred in 17 patients (11 per cent). Thirty-eight patients (24 per cent) underwent reoperation for sepsis, haemorrhage or fistula. Among the 109 survivors, 67 required operation for re-establishment of continuity, at a mean time of 60 days after the first operation, with no difficulty in terms of dissection. No trace of the mesh could be found, other than a criss-cross pattern printed on the deep aspect of the abdominal wall, where the peritoneal surface was fully restored.

Risk factors for wound infection after colorectal surgery: a multicentre study

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Recently, authors from the Centres for Disease Control (CDC) described an individual risk index of surgical wound infection (SWI) that included American Society of Anesthesiologists (ASA) score before operation, duration of surgery, and wound surgical class (contaminated or dirty). This index allows comparison of SWI rate among institutions or surgeons.

A prospective study was conducted between May 1992 and July 1993 in 18 surgical centres. All patients undergoing scheduled colorectal surgery were included and followed until discharge for SWI. CDC definitions of SWI were used. Parameters recorded were age, sex, length of hospital stay before operation, surgery and prophylactic antibiotic duration, ASA score, wound classification and type of surgical procedure.

Among 881 patients included, 159 SWIs were observed in 142 patients (16 per cent): 85 superficial wound infections, 46 cases of intra-abdominal sepsis and 28 anastomotic leakages. Significant risk factors for SWI in univariate analysis were: ASA score of more than 3 (relative risk 1·65; 95 per cent confidence interval 1·25–2·72), abdominoperineal resection (APR) (1·88; 1·27–3·84), PHS (1·97; 1·49–3·27), duration of surgery more than 175 min (1·77; 1·36–2·85), duration of prophylactic antibiotics (1·39; 1·02–2·17) and surgical centre (2·16; 1·68–3·65). Multivariate analysis documented that PHS ($P < 0{\cdot}0001$), duration of surgical procedure lasting more than 175 min ($P < 0{\cdot}001$), APR ($P < 0{\cdot}05$), ASA score of more than 3 ($P < 0{\cdot}03$) and surgical centre ($P < 0{\cdot}00001$) were independent risk factors.

This study confirmed two of the three risk factors for CDC risk index score (ASA score and duration of surgical procedure) and documented two other independent risk factors (APR and PHS) which could be more predictive of SWI for an individual patient.

Inflammatory response in the treatment of experimental peritonitis with granulocyte macrophage-colony stimulating factor

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In this laboratory granulocyte macrophage-colony stimulating factor (GM-CSF) was able to reduce mortality rate from 75 to 23 per cent in a model of sepsis in rats. In this model the authors investigated the capacity of GM-CSF to modulate the inflammatory response in the lungs and liver.

Peritonitis was induced by caecal ligation and puncture (CLP) in Sprague–Dawley rats. Rats were divided into three groups and were killed at two different times (6 and 12 h): group 1, CLP; group 2, CLP + tobramycin 3 μg g^{-1} day^{-1} + clindamycin 40 μg g^{-1} day^{-1}; and group 3, CLP + antibiotics + GM-CSF 1 ng g^{-1} day^{-1}. Tumour necrosis factor (TNF) was measured in the serum and after homogenization in the liver by bioassay. Myeloperoxidase (MPO) was determined in the lung.

In group 1, mean(s.d.) TNF in serum increased to 150(43) pg ml^{-1} at 6 h. Antibiotic treatment did not reduce serum levels (176(46) pg ml^{-1}), while in group 3 the increase in TNF was reduced to 74(27) pg ml^{-1} ($P < 0{\cdot}05$). At 12 h there was no difference between the groups. Furthermore, at 12 h, GM-CSF was able to significantly reduce ($P < 0{\cdot}05$) the increase in liver TNF from 5·56(1·61) ng per ml per g liver in group 1 and 3·40(0·72) ng ml^{-1} g^{-1} in group 2 to 1·1(0·47) ng ml^{-1} g^{-1} in group 3. MPO increased significantly in the lungs of rats with sepsis; at 6 h there was no difference between the groups, but at 12 h the level of MPO in rats treated with GM-CSF was significantly lower (mean(s.d.) 182(16) ΔA per min per g lung; $P < 0{\cdot}05$) than in the rats treated with antibiotics (234(15) ΔA min^{-1} g^{-1}) and the untreated ones (CLP) (230(24) ΔA min^{-1} g^{-1}).

These data suggest that the observed reduction in the mortality rate in this experimental sepsis model may be related to a reduction in the inflammatory response in lungs and liver after GM-CSF treatment.

Calcium alginate and povidone iodine packs in the management of infected postoperative wounds: results of a randomized study

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Abscesses are traditionally treated by incision and drainage followed by packing with gauze soaked in povidone iodine or an antiseptic solution. However, recent experience suggests that alginates are of significant benefit in the management of infected wounds.

A multicentre randomized study was carried out in seven military hospitals to compare the efficacy and safety of these two dressings after incision and drainage of pilonidal abscesses. Seventy patients (37 and 33 in each group) were evaluated weekly (clinical observation, area tracings, wound cavity volume, bacterial swabs and photographs) during a 3-week follow-up.

The mean wound surface reduction in the alginate group was higher at weeks 1, 2 and 3 ($P < 0·05$) and more patients completely filled their wound cavity in the group given alginate (22 *versus* 16; P not significant). There was no difference between the bacteria cultured in the two groups but the calcium alginate rope was painless ($P = 0·0001$) and easier to use ($P = 0·011$) than povidone iodine (using visual analogue scales).

These results confirm that calcium alginate rope is effective and can be used safely in the management of infected wounds.

Effect of modifying the structure and organization of an intensive care unit on postoperative infection: a prospective study

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A prospective study was conducted to evaluate the incidence of postoperative infection in an hepatobiliary surgery and liver transplantation intensive care unit (ICU). The infection rate in two ICUs within the same hospital in similar populations within two periods was compared: between March and September 1992 in a pre-existing ICU (ten beds and five rooms), and between March and September 1993 in a new ICU built within a new hepatobiliary building in the same hospital (15 beds and 15 rooms).

There were 127 patients (78 men, 49 women) with a mean age of 48·8 years admitted to the old ICU, and 225 patients (141 men, 84 women) with a mean age of 51·1 years admitted in the new unit. Among these patients, 65 were admitted for liver transplantation in 1992 and 72 in 1993. Mean(s.d.) duration of stay was 16(43) and 9(13) days respectively in the old and new ICU. The rate of patients infected in the new ICU (31 of 225 (13·8 per cent)) was significantly lower ($P < 0·04$) than that observed in the old ICU (28 of 127 (22·0 per cent)). Similarly, the rate of infection per admission was significantly lower: 43 per cent in 1992 and 24 per cent in 1993. The rate of infection per admission according to the site of infection was respectively in 1992 and 1993: blood positive cultures, 12·6 *versus* 4·4 per cent; catheter, 3·9 *versus* 3·1 per cent; pulmonary, 8·7 *versus* 6·2 per cent; urinary, 3·1 *versus* 4·4 per cent; and colonization of the surgical site, 15·0 *versus* 6·7 per cent. There was a correlation between the number of health care workers present monthly in the ICU and the incidence of nosocomial infections.

In conclusion, restructuring an ICU in terms of architecture, environment and nursing organization adapted to patient population and pathology could reduce the incidence of postoperative infection.

Long-lasting bacterial translocation and dissemination in a rat model after administration of a single dose of endotoxin

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Bacterial translocation has been defined as the passage of viable bacteria from the intestinal tract to the mesenteric lymph nodes (MLN) and further dissemination to other organs after major injury. Enteral feeding has been proposed to reduce protein catabolism, preserve gut mucosal integrity, restore immune dysfunction and therefore decrease the incidence of sepsis. The authors have developed an experimental model which exhibits bacterial translocation and dissemination for at least 3 days, the time necessary to study the efficiency of nutritional support.

Wistar rats underwent selective intestinal decontamination with amoxycillin, streptomycin, vancomycin and amphotericin B for 4 days before intragastric inoculation with a strain of *Escherichia coli* (day 0). This strain was isolated from a blood culture in a patient with burns shortly after injury. On day 2, rats were injected intraperitoneally with endotoxin (ETX) from *E. coli* ATCC 12740 3 mg kg^{-1} or saline (controls). After enteral nutrition from day 3 to day 5 (210 kcal kg^{-1} day^{-1} and 1·18 g nitrogen per kg per day), animals were sacrificed and organs cultured to determine the incidence and magnitude of bacterial translocation.

	MLN		Spleen	
	No. infected	c.f.u. g^{-1}	No. infected	c.f.u. g^{-1}
Control	3 of 6	27 (17)	0 of 6	—
ETX-treated	5 of 5	220 (114)*	4 of 5*	34 (32)

	Liver		Nitrogen balance (mg nitrogen per 3 days)
	No. infected	c.f.u. g^{-1}	
Control	0 of 6	—	6·2(27·2)
ETX-treated	2 of 5	56 (23)	96·4(60·5)*

Values are mean(s.d.). c.f.u., Colony forming units. $^{*}P < 0·05$ *versus* control

The hypercatabolism after injury, displayed by a negative nitrogen balance, did not enhance the incidence of bacterial translocation to MLN, which could be related to bacterial intestinal overgrowth or a putative virulence factor. However, the magnitude of bacterial translocation and dissemination through the organism appeared to be a complication of injury, perhaps due to ETX-induced immunological failure. This model is therefore suitable for further nutritional studies.

Risk factors for nosocomial infection following laparoscopic cholecystectomy in uninfected cholelithiasis without antibiotic prophylaxis

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Analysis of ten preoperative and five operative variables has been undertaken from a prospective study of patients undergoing laparoscopic cholecystectomy without antibiotic prophylaxis to identify patients who could benefit from prophylactic antibiotic cover.

The study included 188 patients analysed over 14 months. The information collected included demographic characteristics, medical risk factors, past history of biliary infection or previous sphincterotomy. Postoperative infections were considered according to the Centres for Disease Control definitions. Postoperative follow-up was 6 weeks.

The incidence of deep incisional wound infection was 2·9 per cent. The overall complication rate was 8·6 per cent. After monovariate analysis, wound infection was independent of all the risk factors in biliary tract surgery and of the operator. Peroperative contamination appeared as a potential risk factor (relative risk 7·5, $P = 0·06$). After multivariate analysis, past biliary infection and peroperative contamination were predictive of postoperative morbidity. Sixteen patients underwent conversion to conventional open cholecystectomy. The incidence of wound infections without antibiotic prophylaxis was 22·2 per cent compared with zero for patients who received a single dose of cefamandole at the time of the conversion.

Antibiotic prophylaxis appeared not to be needed for laparoscopic cholecystectomy, even in patients with risk factors. It should be limited to patients with peroperative contamination or those who need conversion to open cholecystectomy.

Infection and outcome is not always related to surgery and liver failure in patients undergoing liver transplantation

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Infection, allograft rejection and surgical complications are the main cause of morbidity and mortality after liver transplantation for end-stage liver disease. This study assessed the incidence of these complications after liver transplantation for familial amyloid polyneuropathy (FAP).

A total of 26 patients with FAP underwent liver transplantation (21 whole and five partial transplantations). There were 11 women and 15 men of mean age 41 (range 28–66) years. The immunosuppressive regimen included cyclosporin in 14 patients, or rabbit antilymphocyte serum for 10 days then cyclosporin for reduced creatinine clearance in 12 patients. The mean(s.d.) number of blood transfusions was 2·7(2) units and of plasma transfusions 3·2(5) units. Eight patients did not receive transfusions. Twenty patients were cytomegalovirus (CMV) positive serologically. The six CMV-negative recipients received grafts from CMV-negative donors. Twelve patients developed acute rejection that resolved in six after treatment with methylprednisolone; three received OTK3 and four received FK506 for corticosteroid-resistant rejection. Ten of 26 patients developed 26 positive blood cultures after liver transplantation (*Staphylococcus aureus*, 18; *S. epidermidis*, five; klebsiella, two; and pseudomonas, one). The site of the infection was the catheter (two), urinary (two), wound (three), skin sore (one) and unknown (two). Pulmonary infection occurred in four patients, seven developed a wound infection and five a fungal infection. CMV infection occurred in six patients and CMV disease in four. Two patients developed *Pneumocystis carinii* infection. The actuarial survival rate was 77 per cent at 1 year. Six of the 26 patients died 12–160 days after liver transplantation. The cause of death was sepsis in four.

In conclusion, despite a low rate of surgical complications and transfusions for patients with FAP transplanted with normal liver function, the outcome is mainly affected by the high incidence of infection (77 per cent).

Postoperative peritonitis originating in the stomach, duodenum and oesophagus: operative management by intubation and intraluminal irrigation

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In postoperative peritonitis arising from the stomach, duodenum or oesophagus, primary closure commonly fails and intubation alone may be followed by local complications due to the enzymatic action of the gastroduodenal secretions. A new procedure has been designed to neutralize the digestive secretions and achieve efficient drainage from the leaking organ.

Sixty-eight patients with severe postoperative peritonitis originating from leaks in the stomach ($n = 17$), oesophagus ($n = 7$) and duodenum ($n = 44$) were reviewed. Single abscesses accessible to percutaneous drainage or simple surgical drainage only were excluded. Eighty four per cent had at least single organ failure.

Operation included complete debridement of the peritoneal cavity, lavage, capillary drainage, intubation of the leaking organ and primary closure. A three-channelled drain was inserted through the fistula into the bowel lumen, and extraluminal drains were placed near the leakage site. Infusion was undertaken immediately after operation, through the infusion channel of the drain. The fluid was collected by the central line of the intraluminal drain and by the extraluminal tubes. A Witzel jejunostomy was used for enteral nutrition.

The mortality rate was 32 per cent. Reoperations were required in seven patients (10 per cent). Recurrent abscesses occurred in six patients (9 per cent). The mean duration of intubation was 28 days. The fistula resulting from this technique healed spontaneously in 32 patients, while 14 patients required reoperation.

Intubation with continuous endoluminal irrigation successfully prevents local complications by preventing diffusion of septic or enzyme-rich fluids, and allows evacuation of the leaking digestive secretions.

Granulocyte colony stimulating factor and antibiotics in postoperative sepsis prophylaxis

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All recent trials in sepsis using different anti-inflammatory strategies have failed. One possible reason is the underestimated interaction of anticytokine strategies with other prophylactic and therapeutic interventions. The combined effect of recombinant human granulocyte colony stimulating factor (G-CSF) and different antibiotics was studied.

Randomized studies with male Wistar rats were performed to assess the prophylactic use of G-CSF in combination with several antibiotics. All animals were anaesthetized, subjected to laparotomy and peritonitis was induced with human stool. Each antibiotic was tested with and without G-CSF $50\,\mu g\,kg^{-1}$ administered 12 h before operation. The antibiotics were applied 1 h before and after operation: co-amoxiclav $10\,mg\,kg^{-1}$, cefuroxime $10\,mg\,kg^{-1}$ + metronidazole $3·5\,mg\,kg^{-1}$, ceftriaxone $10\,mg\,kg^{-1}$ + metronidazole $3·5\,mg\,kg^{-1}$ and amikacin $25\,mg\,kg^{-1}$ + metronidazole $5\,mg\,kg^{-1}$.

In the control group (no antibiotics) all animals died. All antibiotics reduced the mortality rate, but a further significant ($P < 0·05$) reduction was obtained only by the combination of G-CSF with co-amoxiclav (from 60 to 20 per cent) and cefuroxime/metronidazole (from 50 to 17 per cent). In combination with ceftriaxone/metronidazole the mortality rate was unchanged.

G-CSF reduced the mortality rate only in combination with co-amoxiclav and with cefuroxime/metronidazole. In future clinical trials, the antibiotic regimen must be restricted to antibiotics that produce an increase in survival in combination with recombinant factors.

Alteration of the delayed hypersensitivity response in patients with colorectal tumours

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This prospective study was carried out over a 10-year period (1984–1993) on 267 patients who underwent elective surgery for colorectal cancer (152 men and 115 women; mean age 67·2 years) and 59 healthy control subjects (30 men and 29 women in good physical condition; mean age 63·7 years).

In the 267 patients and 59 controls Multitest IMC (Merieux, Miami, USA) was used to evaluate the immune response: patients were considered to be immunocompetent with a score greater than 10 mm in men and more than 5 mm in women; relatively anergic, with a score of 2–10 mm in men and 2–5 mm in women; and anergic, with a negative response or a score of less than 2 mm.

Immunocompetence was found in 76 per cent of the controls but only 43 per cent of the patients ($P < 0{\cdot}001$). In all, 14 controls (24 per cent) and 145 patients (54·3 per cent) presented with either anergy or relative anergy ($P < 0{\cdot}001$). Tumours located in the caecum were associated with the greatest index of anergy (61·9 per cent) compared with 33 per cent for colonic tumours, 20 per cent for sigmoid lesions and 22·4 per cent for rectal cancers ($P < 0{\cdot}001$).

Patients with colorectal cancer present a high index of lack of delayed hypersensitivity response; in addition, clear differences were found in the index of anergy depending on the anatomical site of the tumour.

Inflammatory activity of the peritoneum: morphological parameters

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The morphology of the inflammatory activity of the peritoneum has been measured qualitatively but quantitative assessments are not common.

In a standardized rat model ($n = 53$) chronic peritoneal abscess was induced by inoculating 10^9 colony forming units per ml *Bacteroides fragilis*. The morphological inflammatory activity was measured qualitatively by histologically proven abscesses and quantitatively by staining the specimen of peritoneum with naphthol-AS-D-chloracetate-esterase (AS-D). Animals were examined on days 3, 7 and 14.

Intra-abdominal abscesses were diagnosed in two of 17, 13 of 18 and 12 of 18 animals on days 3, 7 and 14 respectively. The cytoplasm of granulocytes and tissue mast cells was stained red, so these cells could be counted. On days 3, 7 and 14 respectively, 1·6, 2·8 and 3·4 per cent of the cells were AS-D positive in the omentum *versus* 0·6, 0·9 and 1·4 per cent in controls. Inside the abscesses nearly 100 per cent of the cells were AS-D positive, whereas in the abscess membrane the AS-D-positive rate was 1·6, 12·9 and 11·5 per cent on days 3, 7 and 14 respectively.

The qualitative histological evidence of morphological inflammatory activity of the peritoneum in form of an abscess can be supplemented with quantitative data. AS-D staining can be used to estimate the proportion of granulocytes and tissue mast cells in the inflamed tissue and the inflammatory activity inside the abscess, in the abscess membrane and in non-abscess forming regions.

Can bacterial translocation in aortic aneurysm repair be influenced by oral antibiotics?

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The authors have demonstrated that endotoxin is released during aortic aneurysm repair. It is known that endotoxin may cause a systemic inflammatory response leading to multiple organ dysfunction syndrome. This study investigated the effect of preoperative oral antibiotic administration on endotoxin release and the inflammatory response in a randomized study.

Seven patients given oral ofloxacin and standard perioperative prophylaxis were compared with eight controls who received only standard perioperative antibiotic prophylaxis. Blood samples were obtained before surgery, 30 min after start of operation, 30, 60, 90 and 120 min after clamping the aorta, 4 and 8 h after operation, and on days 1–5 after surgery. Endotoxin was determined by a kinetic limulus amoebocyte lysate assay with internal standardization. Interleukin (IL) 6 was determined by a commercially available enzyme-linked immunosorbent assay.

There were two postoperative complications in each group. Endotoxin was detectable 30 min after clamping of the aorta (mean(s.e.m.) 1·7(1·1) pg ml^{-1}) and remained in the circulation up to 4 h after operation. IL-6 was increased 60 min after clamping of the aorta and maximum levels were observed on the first day after operation (mean(s.e.m.) 260(160) *versus* 174(76) pg ml^{-1} for patients given ofloxacin and controls respectively). There were no differences in endotoxin and IL-6 levels in the two groups.

Either ofloxacin may not influence bacterial translocation during aortic aneurysm repair or endotoxin may be released during operation by other mechanisms which cannot be prevented by ofloxacin. Further studies are needed to establish the clinical significance of bacterial translocation.

Data presentation in the surgical intensive care unit: development of a data presentation system for critical biochemical variables and scoring systems

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The authors have recently developed a computer system for handling results from assays of key components of the plasma cascade systems determined by chromogenic peptide substrate analysis. This system has now been developed further and also incorporates results from blood gas samples, results from key parameters from the hospital main routine clinical chemical tests and vital data from the monitors connected to patients in the intensive care unit.

Indices in established scoring systems, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Sepsis and Acute Physiology II, are calculated and displayed. The Proenzyme Functional Inhibition (PFI) index calculated from chromogenic peptide substrate analysis can be compared with these more common indices. These indices, as well as graphs displaying the development of single parameters, are easily selected and presented.

The system automatically supports established scoring systems as well as the PFI score index. In addition, extreme care has been taken to make it convenient to detect trends in the development of parameter or index values. The present system is regarded as a contribution to the growing concept of paper-free intensive care units.

Sequential treatment of infected pancreatic necrosis with zipper abdominal re-explorations, open abdomen and continuous lavage

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Improved survival of patients with infected pancreatic necrosis (IPN) has been obtained using either open treatment or continuous lavage; the mortality rate, however, ranges between 20 and 70 per cent. The clinical outcome of 14 patients with IPN treated with a combination of open treatment and continuous lavage is reported.

Fourteen consecutive patients (ten men, four women; mean(s.d.) age 54(10) years) with bacteriologically proven IPN were treated by the same surgical team with (1) abdominal re-exploration through a zipper for 7–10 days; (2) open abdomen and debridement for the following 7–10 days; (3) continuous lavage with drainage until resolution of infection; and (4) wound closure. Initial severity of IPN was assessed by computed tomography (infected necrosis less than 30 per cent in three patients, 30–50 per cent in eight and more than 50 per cent in three), Elebute–Stoner sepsis score (mean(s.d.) 16(5)), and by Goris score for multiple organ failure (MOF) (mean(s.d.) 5(1)).

Patients underwent mean(s.d.) 9(4) abdominal re-explorations.

Subsequent continuous lavage lasted 15–85 days; no patient required further re-exploration. The mortality rate was three of 14 patients (21 per cent), because of MOF. The 11 survivors (79 per cent) were discharged with closed abdominal wounds, feeding orally, after a mean(s.d.) of 79(34) days; none had fistulas.

With combined sequential use of abdominal re-exploration, open drainage and continuous lavage, in a consecutive series of patients with severe IPN, the mortality rate was 21 per cent.

Teicoplanin: intraoperative pharmacokinetics and penetration into cardiac and mediastinal tissues

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The concentration of teicoplanin in serum, and mediastinal and heart tissues of 25 patients undergoing cardiac surgery was measured after two regimens of teicoplanin administration. Intraoperative pharmacokinetic parameters were also obtained.

Patients were randomized into two groups: those in group 1 were given teicoplanin 6 mg kg^{-1} intravenously at time of induction of anaesthesia; patients in group 2 were given teicoplanin 12 mg kg^{-1} at the same period. Teicoplanin was assayed by high-pressure liquid chromatography.

C_{max} after teicoplanin 12 mg kg^{-1} was twice that after 6 mg kg^{-1} (mean(s.d.) 134(58) *versus* 64(25) mg l^{-1}). No difference in MRT (mean(s.d.) 8·3(3·3) *versus* 10·8(5·7) h) and T1/2b (mean(s.d.) 7·4(2·7) *versus* 9·4(3·8) h) was observed. Teicoplanin penetrated mediastinal and heart tissues with the exception of sternal bone where the antibiotic was detectable in only two patients. In group 1, five of six patients had tissue concentrations of teicoplanin (other than in sternal bone) less than the MIC90 for potential pathogens that cause infection after cardiac surgery. All patients in group 2 had tissue concentrations of teicoplanin (other than in sternal bone) far in excess of the MIC90 for the potential pathogens.

Teicoplanin 12 mg kg^{-1} penetrates heart and mediastinal tissues readily (with the exception of sternal bone) and reaches tissue levels allowing potent activity against potential pathogens that cause infection following open heart surgery.

Selective decontamination of the digestive tract limits elemental diet induced microbial translocation and restores gut mucosal immunity

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Total parenteral nutrition (TPN) and elemental diet cause Gram-negative bacterial overgrowth and impair gut mucosal immunity thus promoting translocation to the mesenteric lymph nodes (MLN).

Three groups of 15 rats each were isocalorially fed either standard chow (group 1), oral TPN solution (group 2), or oral TPN plus tobramycin 20 mg l^{-1} and polymyxin E 25 mg l^{-1} (group 3). After 7 days, the MLN were removed for analysis of translocated bacteria, the caecum for overall aerobic and Gram-negative enteric bacteria and the intestine for both soluble and insoluble fractions of secretory immunoglobulin A (sIgA).

Group 2 showed significantly increased translocation (53 per cent) compared with groups 1 (7 per cent) and 3 (0 per cent) and the Gram-negative bacteria were 3·4 log more in rats given oral TPN than in the other two groups. The total aerobes were increased by 1·8–2·3 log. In group 2 the insoluble jejunal sIgA was reduced to one-sixth and the insoluble ileal sIgA to one-third of that in the other two groups. The soluble sIgA in group 3 was threefold higher, and that in group 1 twofold higher, than that in group 2.

Selective decontamination prevents Gram-negative caecal overgrowth and translocation to the MLN in a rodent model of oral TPN. The significantly reduced mucosal immunity due to oral TPN is restored by selective decontamination.

Toxic shock syndrome toxin 1 producing *Staphylococcus aureus* after hepatoportal surgery: report on three patients

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Localized infection with multiple organ failure (MOF) associated with methicillin-sensitive *Staphylococcus aureus* (MSSA) was first described in the late 1970s and within 2 years an explosive increase in the number of cases of toxic shock syndrome (TSS) associated with the use of menstrual tampons was reported. Few cases of TSS have been associated with surgical procedures.

The first three cases (one woman, two men) of TSS toxin 1 after hepatic or portal surgery (splenectomy and splenorenal anastomosis, left hepatectomy for colonic cancer metastasis, segmentectomy for hepatocellular carcinoma in a cirrhotic patient) are reported. Septic shock and MOF occurred on day 2 in two patients. MSSA was present in ascites in the first patient, in the surgical wound in the second and in an intra-abdominal abscess in the third. Antimicrobial susceptibility, phage group, toxin identification and endonuclease analysis of plasmids were similar for each strain. Despite resuscitation and surgical debridement two patients died; the survivor was the only one to be treated with steroids and immunoglobulins.

An epidemiological case–control study done by the Infection Control Committee of the hospital failed to find any transmission from person-to-person or contamination by devices during or after surgery. The three patients were not hospitalized during the same period. It is unknown whether these patients had colonization of a TSS-producing strain of MSSA before admission to the hospital or if they acquired the organism during their hospital stay.

Usefulness of bacteriuria and candiduria without leucocyturia in predicting peritonitis after laparotomy

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Intra-abdominal postoperative sepsis is still a diagnostic and therapeutic challenge. The authors have performed a retrospective study to evaluate the significance of bacteriuria and candiduria with regard to the diagnosis of peritonitis after laparotomy.

Between 1 December 1991 and 31 December 1993, 21 patients were admitted to the intensive care unit after 'clean' ($n=19$) or 'contaminated' ($n=2$) laparotomy. All underwent a second laparotomy for suspicion of intra-abdominal septic complications. Intra-abdominal infection was documented or ruled out by the second laparotomy a mean(s.d.) of 13(6) days after the first operation. Infection was present in 13 patients (group 1) and absent in eight (group 2). Urethral catheterization was always performed just before the first operation and the catheter remained in place during hospitalization.

The occurrence of bacteriuria and candiduria was higher in group 1 (eight of 13) than group 2 (one of eight) ($P=0·037$). Specificity of intra-abdominal sepsis when bacteriuria and/or candiduria was present was 88 per cent, sensitivity 62 per cent, and positive and negative predictive values 89 per cent and 58 per cent respectively. In ten patients in group 1 the presence of urinary micro-organisms was remarkable because of the absence of significant pyuria (more than ten leucocytes per mm^3). In group 1, seven of the eight patients with a positive urinary culture had at least one organism isolated.

Isolated bacteriuria and/or candiduria after laparotomy may be considered as an early marker of intra-abdominal septic complications. In such conditions, the absence of pyuria may indicate a transient haematogenous, lymphatic or direct colonization of urine from the intra-abdominal septic focus.

British Journal of Surgery 1996, 83, 865–875

Correspondence

Renal transplantation from non-heart-beating donors

Sir

I read the article by Mr Nicholson (*Br J Surg* 1996; 83: 147–8) regarding non-heart-beating organ donation with great interest. The introduction of such a scheme may well provide many additional valuable organs for transplantation, and I would commend the Leicester group for their foresight and commitment to this method of procuring organs.

Several years ago I was involved in drawing up a protocol for a similar scheme. During this exercise I consulted widely regarding the ethical and practical issues involved. As in all other methods of organ procurement, it is of vital importance that there are no controversial elements that can be seized upon by the anti-organ-donation lobby. I was therefore alarmed to read that the introduction of cardiopulmonary resuscitation was being advocated in asystolic donors. I believe that this must not be a part of the technique used.

An understanding of the differences between the traditional diagnosis of death and brain stem death is necessary to appreciate the importance of this point. The traditional diagnosis of death is based on the cessation of respiration and circulation. In this circumstance there is no attempt to diagnose brain stem death, and indeed it would not be possible to do so under present criteria. That the cessation of circulation and respiration is permanent is inherent to the diagnosis and crucial to its validity. Only with this assumption can we be sure that the brain will not recover function.

The diagnosis of brain stem death is based on the demonstration of the absence of brain stem functions in the circumstances of other specified criteria. In this situation we allow the continuation of circulation and artificial respiration because it is certain that there is no consciousness, nor the possibility of consciousness according to our understanding of the functions of brain stem structures.

The protocol described by Mr Nicholson includes the diagnosis of death by traditional methods followed by cardiac massage and mechanical ventilation with 100 per cent oxygen to prevent ischaemic damage to the organs that are to be retrieved. By the same token, circulation of oxygenated blood to the brain will occur, and it is therefore not possible for the diagnosis of death to be sustained. One can argue that sufficient ischaemic time may have elapsed for it to be highly unlikely that consciousness could return; however, there is no evidence as to what length of time would be necessary for certainty.

The main point of all this is that the public, whom we ask to accept the things we do in the quest for organs for transplantation, must be able to be absolutely assured of the diagnosis of death in the patients who act as donors.

A long battle has been fought to make the criteria of brain stem death accepted. This argument has been won because of the incontrovertible logic of the case. There is a very real danger that much of this ground could be lost by the introduction of an ill conceived protocol for retrieving organs from asystolic donors.

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Author's reply

Sir

Thank you for allowing me the opportunity to respond to Mr Ferguson's criticisms of the Leicester non-heart-beating programme. The main point to be addressed is the use of what Mr Ferguson calls 'cardiopulmonary resuscitation ... in asystolic donors'; this of course is a *non sequitur*. As death will already have been pronounced, attempts at resuscitation have, by definition, been abandoned. The process then carried out is external cardiac massage and ventilation of the cadaver. The difference may appear to be semantic, but an examination of the stages involved will show that this is not the case. After death has been pronounced and recorded in the hospital notes, external cardiac massage and ventilation are stopped for a period of 10 min. Heart massage and ventilation with 100 per cent oxygen are re-started in an attempt to oxygenate the kidneys until *in situ* cooling is achieved. The 10-min period allows everyone involved to appreciate that the patient is dead and is now being considered only as a potential organ donor, i.e. not receiving 'resuscitation'.

The diagnosis of death in this situation is made by the most senior clinician responsible for the patient, and only then can the possibility of organ donation arise. The doctors diagnosing death are completely independent from the transplant team. In Leicester the transplant team even work in a separate hospital 3 miles away from the accident unit.

The definition of death has always caused some clinicians to become confused, and Mr Ferguson's letter does nothing to clarify the accepted position in our society. To paraphrase Pallis[1], there is only one type of human death: an irreversible loss of the capacity for consciousness coupled with an irreversible loss of the capacity to breathe. As both these functions are subserved by the brain stem, the only kind of human death is 'brain stem death'. This may arise from an intracranial event such as bleeding or it may be secondary to extracranial events such as circulatory arrest. It is accepted that 4 min of circulatory arrest causes an irreversible period of cerebral anoxia, and the 10-min period without cardiac massage or ventilation accounts easily for this. I would agree that the public must have complete confidence in the rectitude of any organ donation. In Leicester the proposed non-heart-beating donor programme was widely publicized before its introduction. This publicity included an open letter in the local press asking for any objections; there were none. The only feedback we have received from the relatives of non-heart-beating donors has been positive.

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Long-term results of giant prosthetic reinforcement of the visceral sac for complex recurrent inguinal hernia

Sir

We were pleased to read the important contribution by Dr Beets and colleagues (*Br J Surg* 1996; 83: 203–6). Like the authors we repair virtually all recurrent hernias, single or bilateral, with a large properitoneal prosthetic mesh (giant prosthetic reinforcement of the visceral sac), using the method of Stoppa *et al.*[1] or Wantz[2].

We make the following comments about the operation based on our experience of 65 patients. The operation originated by Professor Stoppa requires an approach that is not immediately familiar to all general surgeons; this fact probably accounts for its limited acceptance in the UK. It also has a long learning curve. However, we have been impressed by rapid recovery after operation and excellent short-term results.

The conventional anterior approach for recurrent hernia has a well documented high recurrence rate of 15–30 per cent[3], as well as an increased risk of testicular vessel damage of up to 5 per cent[4]. The likelihood of vascular damage is virtually eliminated with the properitoneal approach, and we have encountered no testicular complications in any of our patients.

All our patients had general anaesthesia. They were not catheterized but were instructed to empty their bladders immediately before operation. All patients were discharged after one night in hospital, the suction drain having been removed. Bilateral recurrences were approached via a vertical midline or a horizontal suprapubic approach, the latter giving less discomfort. For unilateral recurrences, a high transverse inguinal incision was used from just below the anterior superior iliac spine to the midline[2]. We used Mersilene (Ethicon, Edinburgh, UK) rather than Marlex (C. R. Bard, Billerica, Massachusetts, USA) mesh because of its flexibility and have adopted the Stoppa technique of parietalizing the cord and testicular vessels after dissecting them away from the peritoneal sac. We did not make a vertical slit in the upper border. No attempt was made to close the hernia defect, but with recurrences of more than 2·5 cm in diameter, or when the inguinal ligament was absent, the gap was buttressed by a polypropylene mesh patch. The placement of the large mesh measuring 25 × 15 cm needed hands-on positioning to achieve its aim of covering the wide area of potential herniation in an anatomical situation of many curves.

Postoperative problems have included two short-term immediate recurrences within 1 week, reflecting technical factors early in the series. No subsequent or late recurrence has occurred, and there have been no cases of infection. Patient acceptance has been high, and physical activities, especially walking and cycling, have been encouraged from the first day.

Like Dr Beets and colleagues, we believe that recurrent hernia, particularly multiple hernias, should no longer be repaired by an anterior approach, with the exception of recurrence following laparoscopic repair, small medial defects in the aged or those unsuitable for general anaesthesia. Unlike Dr Beets and colleagues, we believe wide access is necessary to ensure multiple points of simultaneous pressure to achieve accurate moulding of the mesh into multicurved areas. The laparoscopic approach does not permit this to be done.

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Author's reply

Sir

We were pleased to read about Mr Kark's favourable experience with the giant prosthetic reinforcement of the visceral sac (GPRVS) procedure for recurrent hernias. Whether laparoscopic hernia repair can achieve the same low recurrence rate indeed remains to be proved. We are pleased to inform Mr Kark and his colleagues that, so far, we have included 80 patients in a randomized trial comparing GPRVS with laparoscopic repair for recurrent inguinal hernia. The results of this trial may shed some light on the issue.

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Balloon tamponade for control of massive presacral haemorrhage

Sir

I read with interest the case report by Mr McCourtney and colleagues (*Br J Surg* 1996; **83**: 222) on control of massive presacral haemorrhage. However, I am surprised that, after reporting their anecdotal experience with one patient, the authors enthusiastically conclude that this 'may be the best method of controlling haemorrhage' in such instances. In fact, it would be interesting to verify for more than one patient the risk of secondary, life-threatening haemorrhage once the balloon is deflated. In any case, while not disputing the role of perineal tamponade as such (by means of a Sengstaken–Blakemore tube, etc.) it should be stressed that a number of other interventional techniques do exist, including conventional packing, diathermy, stick tie, or even occlusion using bone wax[1]. As the best method of temporarily arresting this type of haemorrhage is represented by simple occlusion of the bleeding point with the index finger, titanium thumbtacks have been developed to achieve the purpose of stable, durable and safe haemostasis[2,3]. This technique has been employed successfully in a number of patients and appears more reliable than temporary balloon tamponade.

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Authors' reply

Sir

We thank Dr Basso for his interest in our article. Although he is correct in pointing out that a variety of techniques can be used to control presacral haemorrhage, he fails to make a distinction between the two recognized types of massive presacral bleeding[1].

Titanium thumbtacks have been described for the control of high-pressure presacral bleeding produced by a tear in the basivertebral vein[1]. This vein traverses the body of the sacrum and communicates between the internal vertebral venous system and external presacral venous plexus in 16 per cent of patients[2]. At operation such bleeding can be controlled in the first instance by pressing the sacrum with a finger over the characteristic dimple of the injured basivertebral venous opening located between S3 and S5. Permanent control is then achieved by sacral application of the thumbtack. Contraindications to this technique include bleeding more than 2 cm from the midline and diffuse presacral haemorrhage[3]. The latter situation was encountered in the patient we reported. Although recognized techniques for dealing with diffuse, massive presacral haemorrhage include packing and/or suturing[1], we reiterate that our experience suggests that balloon tamponade may be the most effective method of achieving haemostasis when other methods fail to control this type of bleeding.

As sacral application of titanium thumbtacks and perineal balloon tamponade control two quite different forms of massive presacral haemorrhage, we believe that comparisons of the two methods and statements regarding which technique is more reliable should be avoided.

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1 Nivatvongs S, Fang DT. The use of thumbtacks to stop massive presacral haemorrhage. *Dis Colon Rectum* 1986; 29: 589–90.
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Diagnosis of arterial disease of the lower extremities with duplex ultrasonography

Sir

I read with interest the paper by Mr Koelemay and colleagues (*Br J Surg* 1996; 83: 404–9) and agree that duplex ultrasonography should replace diagnostic angiography for patients with arterial occlusive disease. With continuing improvements in ultrasonographic technology, the assessment of these patients should only get better in the future.

While we await this new technology, there is a simple manoeuvre that can be used to improve the duplex investigation of aortoiliac disease. The iliac arteries are covered by bowel, and therefore gas and faeces often obscure sections of the aortoiliac segment. Employing an iso-osmotic bowel preparation, a marked increase in visibility of these arteries has been observed[1]. In addition, the time taken to perform a full aortoiliac duplex examination significantly decreased from 52 to 33 min while producing a sensitivity of 94·4 per cent and specificity of 93·4 per cent[2].

Accurate assessment of arterial inflow is essential for successful decision making in the vascular patient. With increasing numbers of patients requiring vascular assessments, time on the duplex ultrasonography machine is at a premium. The use of iso-osmotic bowel preparation is a useful addition to improve the service of the vascular laboratory.

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The retrocaecal appendix appears to be less prone to infection

Sir

Mr Varshney and colleagues (*Br J Surg* 1996; 83: 223–4) have inappropriately concluded that the retrocaecal appendix appears to be less prone to infection. The results of this retrospective study can only permit one to conclude that the retrocaecal position is not the commonest site of the acutely inflammed appendix, and that gangrene and perforation are commoner in retrocaecal appendices. While another large retrospective study has also revealed a higher incidence of perforations and serious complications in acute retrocaecal appendicitis[1], one prospective study[2] and two retrospective studies[3,4] have established that the retrocaecal position of the appendix does not alter the clinical course of acute appendicitis. In these latter studies, there was neither a delay in the diagnosis nor a higher incidence of appendiceal rupture or wound infection in retrocaecal appendicitis. This finding is not unexpected as most retrocaecal appendices remain intraperitoneal[5], and the disease then follows the usual course of appendicitis.

I also take issue with the authors' suggestion that the greater incidence of haematuria and pyuria in patients with retrocaecal appendicitis may lead to under-reporting of retrocaecal appendices, because of a mistaken diagnosis of urinary tract infection. Positive findings on urinalysis have been repeatedly stressed to be distinguishing features of retrocaecal appendicitis[6–8], and are unlikely to lead to a high incidence of misdiagnosis.

Finally, the hypothesis that the retrocaecal position makes the appendix less prone to infection because of gravity-assisted drainage of the luminal contents, although ingenious, is unsupported. The appendix is not always straight, and a single curvature or angulation of this organ may obviate the potential benefit of the retrocaecal position.

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Author's reply

Sir

Mr Sarela states that we are incorrect in concluding that the retrocaecal appendix appears to be less prone to infection than appendices in other positions. I can only reiterate the salient points of our argument. Post-mortem studies have shown that the commonest anatomical position of the appendix is in the retrocaecal position. This position is under-represented among patients with clinical acute appendicitis. This fact could be explained by (1) failure to recognize mild cases of appdendicitis, which may be misdiagnosed as urinary tract infections, treated with antibiotics and resolve, or (2) the hypothesis that the retrocaecal appendix is in some way less prone to obstruction and subsequent appendicitis. Either or both of these explanations may be true in our patients. Our study did not test either of these hypotheses, which were generated from the observed data.

I am pleased that Mr Sarela finds our hypothesis ingenious. Of course an original hypothesis requires independent testing to confirm or refute it. However, a prospective study of appendiceal position and subsequent appendicitis rates would be laborious.

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Open diagnostic peritoneal lavage

Sir

I strongly believe that there is a definite role for diagnostic peritoneal lavage (DPL) in the management of abdominal trauma. However, this role is confined to a well defined select group of patients in whom clinical appraisal and other non-invasive investigative modalities fail to help in decision making. As such, the ability of trauma physicians to perform DPL safely and reliably is mandatory.

I read the article written by Messrs Potter and Paterson-Brown (*Br J Surg* 1996; 83: 87) with immense interest. The authors described a method of cut-down technique of DPL to overcome the problem of poor lighting and limited assistance in the trauma suite. This method is also thought to be expeditious in obese patients. The authors have equated the justification for this procedure to that of the cut-down technique for laparoscopic paraumbilical port insertion. To highlight a few points: this method is performed with the abdomen prepared from xiphisternum to symphysis pubis; the umbilicus is everted using a toothed grasping forceps or towel clip; and the umbilical tube is incised and further blunt dissection through this plane gives access to the peritoneum.

However, I have several reservations about the method described. First, I find it hard to believe that such a trauma centre with poor lighting and limited assistance exists, especially in the UK. From my experience of 'conventional' open DPL and the cut-down technique of laparoscopic umbilical port insertion, the latter can hardly be done alone and, in my opinion, an assistant is mandatory for successful completion, especially in obese patients. It may be quick but may not necessarily be completely blood-free as there will always be some subcutaneous (and preperitoneal) fat that requires cutting, despite the assertion that the skin abuts the peritoneum directly at the umbilical tube. In fact the skin will never abut the peritoneum directly as there will always be a thick fascia between (and separating) them[3]. When performing open DPL, which usually involves only a 3-cm incision, I do not think that the whole abdomen needs to be prepared. I am concerned about the authors' method of everting the umbilical tube. Quite a strong force is usually needed to evert the umbilicus in an upward thrust, so that an ordinary grasping forceps (held in a 'pen-grip') cannot adequately be used to grasp the tissue. A caucus forceps with a racheted handle is most suitable for this purpose.

One can imagine the discomfort caused to a patient who only receives local anaesthetic for the procedure. The main disadvantage of this technique is the inability to perform direct cut down on the peritoneum itself. It is therefore essentially a partially blind technique. By contrast, in the 'conventional' open method there is no upward force required and the peritoneum is grasped by artery forceps and opened directly. Although acceptable in laparoscopic umbilical port insertion for gas insufflation (as compared with Veress needle with blind trocar insertion), this technique is, I believe, inferior to the conventional direct cut-down method performed anywhere along the midline of the abdomen[1–3].

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1 Moore JB, Moore EE, Markovchick VJ *et al.* Diagnostic peritoneal lavage for abdominal trauma – superiority of the open technique at the infraumbilical ring. *J Trauma* 1981; **21**: 570–2.
2 DuPriest RN Jr, Khaneja SC, Rodriguez A *et al.* A technique for open diagnostic peritoneal lavage. *Surg Gynecol Obstet* 1978; **147**: 241–3.
3 Ridgeway CA, Howington JA, McNabney WK *et al.* Expediting the open diagnostic peritoneal lavage. *J Am Coll Surg* 1995; **180**: 735–6.

Authors' reply

Sir

Thank you for the opportunity to reply to Mr Hamid Mat Sain's letter. We have difficulty understanding the point he is trying to make. Our technique is a safe and simple method of performing open peritoneal lavage which has been popularized in many centres throughout the UK for open laparoscopy. The references given by Mr Mat Sain simply support our technique[1–3]; in particular, Ridgeway *et al.*[1] emphasize the advantages of entry into the peritoneal cavity through the umbilical tube where the distance between the skin and the peritoneum is shortest. Mr Mat Sain cannot have worked in many emergency departments in the UK if he does not accept that the quality of lighting is often poor and it may be difficult to gain assistance in performing open peritoneal lavage. In our experience this is often the case in the emergency setting in a busy trauma unit, of which the Royal Infirmary is one, and our technique has the advantage of not requiring assistance or theatre-quality lighting. We were interested to hear that Mr Mat Sein had trouble trying to use the above technique for open laparoscopy as we have not experienced the problems he seems to have encountered.

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Risk-adjusted analysis of surgeon performance: a 1-year study

Sir

With reference to the letter from Mr Copeland (*Br J Surg* 1996; 83: 136) in which he says that 'surgeon A is performing well within his confidence limits and therefore his death rate does not differ from that expected', I feel I should point out that the calculated ratio will always lie within the corresponding confidence interval. The important point to consider is whether the value of 1, which corresponds to no difference between observed and expected deaths, lies within the interval.

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'Residual' appendicitis following incomplete laparoscopic appendicectomy

Sir

With reference to the recent article by Messrs Milne and Bradbury (*Br J Surg* 1996; 83: 217) concerning incomplete removal of the appendix laparoscopically, we know of two patients in whom the appendix was not removed completely at open operation.

In one patient only the terminal portion of the appendix was removed, the proximal portion being 'buried' in the caecal wall. In the other, an appendix epiploica was mistakenly removed instead of the appendix. Both patients developed recurrent or persistent symptoms, and in the presence of a grid-iron incision scar subsequent diagnosis was difficult.

We are sure that there have been many more similar cases over the years and cannot agree that this particular complication is peculiar to the laparoscopic approach.

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Importance of human immunodeficiency virus-associated lymphadenopathy and tuberculous lymphadenitis in patients undergoing lymph node biopsy in Zambia

Sir

Lymphadenopathy is a common finding in patients with human immunodeficiency virus (HIV) infection, ranging from the generalized follicular hyperplasia seen early in the disease, to involvement with secondary opportunistic infections and neoplasms. Dr Bem and colleagues (*Br J Surg* 1996; 83: 75–8) have provided some interesting epidemiological data on the prevalence of tuberculous lymphadenitis in HIV-1 seropositive individuals in central Africa. However, they fail to emphasize that extrapulmonary infection with *Mycobacterium tuberculosis* and Kaposi's sarcoma, when diagnosed definitively regardless of the presence of other causes of immunodeficiency and in the presence of laboratory evidence of HIV infection, are indicator diseases for acquired immune deficiency syndrome (AIDS) (as per the Centers for Disease Control surveillance case definition for AIDS, 1993)[1]. Thus, 157 HIV-seropositive individuals with tuberculous lymphadenitis and 25 HIV-seropositive individuals with nodal Kaposi's disease in this series may be diagnosed as having AIDS. The status of the five HIV-seropositive patients with nodal lymphoma would depend on the histopathological details. While the clinician may view HIV disease simply as a broad spectrum ranging from primary infection, with or without the acute HIV syndrome, to the asymptomatic infected state to advanced disease, a strict definition of AIDS is necessary for epidemiological purposes and surveillance.

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Surgical management of rectal cancer

Sir

Messrs Scholefield and Northover (*Br J Surg* 1995; 82: 745–8) take up an important medical issue for debate, namely the surgical management of rectal cancer. They describe the apparently excellent results achieved at the National Cancer Center Hospital (NCCH) in Tokyo where an extended lymphadenectomy was used. The technique and the results, both in terms of local and general disease control and adverse effects, are clearly described, and the lack of controlled data is acknowledged.

Furthermore, they state that 'it behoves us (surgeons in the West) to examine carefully any techniques that might offer a way of improving on surgical outcome (as done by surgeons at the NCCH)'. This statement is correct only if operation is the only treatment option. Both irradiation and chemotherapy have the ability to kill cancer cells, although their cell kill effect may as yet be regarded as relatively minor. The availability of different treatment modalities behoves us (cancer-treating clinicians throughout the world) critically to examine the advantages and disadvantages of all modalities and then design appropriate trials that test the validity of any (combined) approach aimed at improving overall treatment results (not only surgical outcome).

Advantages and disadvantages of surgical treatment

Operation is likely to remain the most readily available method of removing a large tumour, but it has to preserve important structures in an attempt to extirpate the most remote and invisible tumour cell deposits. In rectal cancer, the most likely reason for local failure is the inability to remove tumour cells at the lateral margins[1].

Advantages and disadvantages of radiotherapy

A radiation dose of about 50 Gy (2 Gy daily, 5 days per week for 5 weeks) or a comparable dose using other fractionation schedules (such as 25 Gy, 5 Gy daily in 1 week) is required to kill with a high degree of probability (more than 90 per cent) microscopic foci of cancer cells[2,3]. As radiation also damages normal cells, the number of tumour cells that can be killed is limited by the dose that can be tolerated by the irradiated normal tissues. The urinary bladder, the rectum itself and other tissues around the rectum tolerate about 60 Gy[4], unless one accepts a probability of severe late adverse toxicity in excess of 5 per cent. Small bowel loops are more sensitive but they tolerate about 50 Gy unless the irradiated small bowel volume is large.

With these probabilities in mind, radiation alone possesses a low probability of curing any tumour in the rectum that is larger than 1 cm in diameter. The likelihood of killing microscopic foci not removed surgically will, however, be high. This likelihood is lower after operation than before; during the delay from diagnosis to the start of radiation after surgery, some deposits could grow beyond the limits of eradication. Clinical studies of rectal cancer have shown that radiotherapy is more dose-efficient when given before than after operation[5,6]. With an appropriate technique, it is possible to deliver a dose of approximately 50 Gy to the entire volume at risk of containing rectal cancer cells within the pelvic cavity while limiting the irradiated small bowel volume[5,6].

Advantages and disadvantages of chemotherapy

In patients with metastatic colorectal cancer, even the best available regimen – biochemically modulated 5-fluorouracil[7] – seldom results in partial remission and extremely rarely in complete remission. In the adjuvant situation, i.e. microscopic disseminated disease, the most optimistic studies now report that mortality rate is reduced by one-third[7]. This fact means that, on average, chemotherapy kills between 2 and 3 log powers of cells. For complete eradication, these foci are then 0·1 mm in diameter at most. The great disadvantage of chemotherapy is therefore its very limited cell kill effect, but its advantage is that it can kill cells throughout the body.

Logic for combining surgery and radiotherapy in rectal cancer treatment

Taking the advantages and disadvantages of these three therapeutic modalities into consideration, the most logical approach would appear to be to combine radiation with operative excision. As the radiation dose must be limited to remain safe, operation has to remove any tumour deposits that are larger than a few millimetres in diameter (at most 10^7–10^8 cells), but with as little functional impairment as possible.

Results from randomized clinical trials have repeatedly shown that preoperative doses of 40 Gy in 4 weeks or comparable doses with other fractionation schedules (e.g. 20–25 Gy in four or five fractions of 5 Gy each) reduce local failure rates in patients receiving conventional surgical treatment by 50–65 per cent[6]. Postoperative radiotherapy at even higher doses (46–60 Gy in 5–7 weeks) is less effective. One explanation why preoperative radiotherapy does not reduce the proportion of local failures still further is that the size of the tumour deposits left after a standard operation may be too large to be eradicated by the given tumour dose. Although the surgical goal is therefore to avoid leaving large tumour deposits, the use of a combined approach may spare the need to remove every single tumour cell.

Standard surgical treatment in the West, which generally results in local failure rates of 25–30 per cent, is not capable of yielding very high (more than 95–98 per cent) local control rates even if combined with adequate radiotherapy[5]. Improved surgical techniques entailing total mesorectal excision (TME), as popularized by Heald and Ryall[8], could be adequate. It is possible, although not proven, that this procedure leaves fewer tumour cells in the pelvic cavity; any residual deposits may also be smaller. When such techniques are combined with preoperative radiotherapy, local failures may be almost entirely eradicated. A formal trial comparing TME with preoperative radiotherapy plus TME has not yet been performed, although a proposal from Holland is presently under discussion (personal communication).

Which is the best treatment option for a patient with rectal cancer? Messrs Scholefield and Northover argue for supraradical resection according to the Japanese experience. We argue that a moderate dose of preoperative irradiation delivered before optimal standard surgery[8] will result in (at least) the same local and overall cure rates, but less morbidity. These two options have not been tested in a controlled clinical trial.

It would be a major step forward if surgical techniques and surgeon skills were improved so that local failure rates were lowered from the current level of 30 per cent, commonly observed in Western centres, to 10–15 per cent, which might be anticipated if TME surgery were used routinely. However, we doubt that the local failure rate of 6 per cent obtained by Heald and Ryall[8] can be emulated in most hospitals.

It is not because of arrogance or ignorance that we have advanced to adjuvant treatment as the most likely way of improving results, as stated by Messrs Scholefield and Northover, but by exploring the advantages and disadvantages of each treatment modality. If arrogance exists, it is in the refusal to realize the disadvantage of a particular technique, i.e. supraradical surgery with its risks of excessive morbidity.

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Cell proliferation kinetics are abnormal in transitional mucosa adjacent to colorectal carcinoma

Sir

We enjoyed the recent paper by Drs Yoshikawa and Utsunomiya concerning the transitional mucosa of the colorectum (*Br J Surg* 1996; 83: 36–9). Transitional mucosa is characterized by increased amounts of sialomucin and elongation of crypts. It is still unclear whether the transitional mucosa is a preneoplastic phenomenon or a reactive change to the adjacent carcinoma[1].

Yoshikawa and Utsunomiya demonstrated that the proliferating cell nuclear antigen (PCNA) labelling index of the middle part of the crypts in transitional mucosa was higher than that of uninvolved mucosa or control mucosa, suggesting an upward shift of the proliferating cells towards the bowel lumen. They believed that this finding may contribute to the abnormal cell development necessary for malignant change and regarded the transitional mucosa as a preneoplastic phenomenon. However, there were no significant differences in the total PCNA labelling indices between normal control mucosa, uninvolved mucosa and transitional mucosa. We have recently reported that mucosal endocrine cells expressing chromogranin A were normally seen in the lower third of the crypt but were shifted towards the bowel lumen in transitional mucosa[2]. Our report and that of Yoshikawa and Utsunomiya only disclose that transitional mucosa has a different distribution of cell compartments from the normal mucosa; there is no direct evidence that transitional mucosa is a preneoplastic phenomenon.

As reported previously[2], we consider that transitional mucosa is more likely to be a secondary phenomenon rather than a preneoplastic one for the following reasons: (1) transitional mucosa is present in patients with benign polyps, not only those with neoplastic lesions; (2) in patients with carcinoma, a transitional mucosa is recognized not only in those typical of an adenoma–carcinoma sequence but also in those cases of suspected *de novo* origin. It is doubtful whether there is the same preneoplastic change in the two pathways. Presently, we therefore consider that the presence of transitional mucosa may not offer a potential screening opportunity for colorectal carcinoma.

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Authors' reply

Sir

Many thanks for giving us the opportunity to reply to this letter.

We agree that transitional mucosa is more likely to be a secondary change of the mucosal phenotype resulting from the host–tumour interactions than a pre-existing change specific to colorectal tumour. However, it was not our intention to describe whether it was a primary or a secondary phenomenon, but to evaluate whether altered cell proliferation kinetics, assessed by proliferating cell nuclear antigen immunostaining, were useful as a possible adjunct in screening for heightened risk for the development of colorectal cancer. We would like to congratulate Dr Mori and colleagues on their informative findings, but we suggest that they convey a similar message to our attempt to bridge the gap between biochemistry and clinical practice.

We are very interested in those with altered antigenicity and morphology who may warrant closer surveillance, such as individuals with a strong family history of colorectal cancer. In this field, subtle cellular changes may be used as an intermediate biomarker in trials of dietary or pharmacological interaction.

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Polite surgeons?

Sir

Surgeons must rank as the most courteous people in the world.

I sometimes work for the UK Cochrane Collaboration hand-searching journals for randomized controlled trials and clinical controlled trials. I have recently had the pleasure of reading the *British Journal of Surgery* for 1995. The pleasure lay in the correspondence. Almost invariably every letter from, say, a Mr Brown opens with an expression of interest (sometimes great, occasionally enormous) in a paper published by Mr Smith. Mr Smith replies to the effect that he is enchanted to be given the opportunity to thank Mr Brown for his great/enormous interest. In between, of course, they fillet the work/criticism in question, but always with the most exquisite courtesy and tact. I contrast this with the hurly-burly correspondence in other respected journals, where often the boots and knuckles are in before the end of the first sentence, heaping scorn and derision and reducing all but the most hardened to tears.

I can hardly imagine that surgeons are exempt from the ghastliness of what has happened and continues to happen to the poor, beleaguered National Health Service, where money and management appear to have become the paramount considerations, but I am curious as to what sets surgeons apart. I have had only one brief (and painful) encounter with a surgeon. I hated him because he clearly regarded me as a nasty little NHS perineal abscess, but my goodness he was jolly polite to the space above my head.

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Management of intestinal obstruction after gastrectomy for carcinoma

Sir

We read with interest the article by Dr Nakane and colleagues (*Br J Surg* 1996; 83: 113), and agree that active surgical intervention is an important option in the management of intestinal obstruction in patients who have undergone gastrectomy for carcinoma. However, we disagree strongly that all patients who do not settle with conservative management should be subjected to laparotomy unless they are terminally ill ('laparotomy not deemed appropriate in 17 of 85 patients due to uncontrolled ascitis or cachexia'). The authors' figures show that of 50 patients who underwent operation only 27 (54 per cent) left hospital. We do not feel it is appropriate that 46 per cent of patients should undergo an unnecessary operation for what is at that stage an incurable condition with potentially unpleasant postoperative complications such as ascitic leak.

It is our policy to be much more selective in such patients, who are first screened by radiology to determine the extent of the malignant process. If suitable at that stage, they undergo laparoscopy. Those patients with peritoneal seedlings undergo biopsy under direct vision and recover without serious complications. Patients with treatable lesions, benign or malignant, are submitted to laparoscopic lysis of adhesions or open procedures to excise local recurrences. We consider that a laparotomy in patients with peritoneal deposits is particularly prone to unpleasant postoperative complications and is without benefit. We also give importance to the operative findings and histology at the time of gastrectomy and obviously would be more aggressive in our management if the procedure was thought to have been curative. We believe that this policy gives a better quality of life to our patients without denying operation.

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Authors' reply

Sir

We thank Dr Dawson and colleagues for their interest in our paper. As stated in the original publication, we showed that of 50 patients who underwent operation, 34 (68 per cent) had symptomatic relief, and 27 (54 per cent) were discharged from hospital.

We consider it is appropriate to choose surgical intervention when symptomatic relief cannot be obtained with conservative management. We are indeed interested in laparoscopic lysis of adhesions. However, it is difficult to treat intestinal obstruction due to malignancy by laparoscopy.

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Mammary duct ectasia–periductal mastitis complex

Sir

I was disappointed by the recent leading article (*Br J Surg* 1995; 82: 1300–2) on mammary duct ectasia–periductal mastitis. There have been several advances in our understanding of this condition which were ignored by the author. The end result was a confused and outdated article which contained several factual inaccuracies.

As the author himself indicates, duct dilatation occurs in 50 per cent of women by the age of 60 years[1], and thus can be considered as normal in this age group rather than a disease (which he is implying). Nipple discharge is described as spontaneous discharge of fluid from the nipple. It is well recognized that gentle compression of the breasts and the nipple ducts will produce fluid from the nipple, but these are physiological breast secretions which are well described products of normal breasts and do not require cytological examination[2,3]. Studies have demonstrated that 70 per cent of premenopausal women can be made to produce nipple secretions[3]. If these secretions are part of what the author describes as nipple discharge, it would be inappropriate to provoke anxiety in these women by requesting cytological investigations.

In relation to squamous metaplasia, Mr Webb indicates this is a developmental abnormality and that it is a cause of periductal mastitis–duct ectasia. This comment is incorrect. Heavy smoking is associated with squamous metaplasia of the ducts, and the squamous metaplasia that occurs may or may not be responsible for the subsequent development of mamillary fistula and periductal abscess[4,5].

The practical points that were provided in this article have little evidence-based research to support them (point 1). If every patient's subareolar terminal ducts were expressed, as stated above, up to 70 per cent would produce breast secretions; these do not require any further investigation, including cytological examination.

Point 2: There is no evidence in the literature that antibiotics help non-cyclical mastalgia.

Point 4: Women with periductal mastitis have multiple duct inflammation, and excision of only a single duct leads to recurrence of infection from periductal mastitis in the surrounding ducts. Thus, when a mamillary fistula has occurred, the most logical operation is fistula excision combined with total duct excision[6].

Point 5: Mr Webb quotes the Bristol experience of major duct excision or fistulectomy after drainage of a subareolar, non-lactating abscess. He describes the success rate as modest, but Lambert *et al.*[7] quoted a highly satisfactory 98 per cent success rate for this operation in similar circumstances. Repeat operation in the series from Manchester was rarely necessary and no patient required mastectomy[6]. In fact, despite over 300 referrals per year in Manchester for periductal mastitis–duct ectasia, no patient has required a mastectomy for the past 10 years.

Point 6: While I agree it is important to beware that this condition can simulate an inflammatory carcinoma and may present with systemic features, fine-needle aspiration cytology is not the only modality to investigate the condition. Mammography is of value in these patients to exclude an underlying cancer. Ultrasonography would also enable effective treatment of extensive multilocular abscesses by image-guided aspiration combined with antibiotic therapy. Total duct excision is best performed once the abscesses and acute infection have been treated.

Point 7: There is little emphasis placed on the role of antibiotics given to patients before operation. It is well recognized that infection after biopsy for this condition is significantly higher than after biopsy for other breast conditions[8]. In the presence of low-grade infection, although wound packing and delayed suture may be acceptable, it is far more efficient to treat the patient with primary closure under antibiotic cover, which results in a successful outcome in most cases. Most patients do not appreciate having to return for weeks or months to a district nurse to have a wound packed[6,8].

Point 10: Most patients who complain of multiple duct nipple secretion have physiological breast secretions and do not have nipple discharge as stated above. While bloodstained discharge requires investigation, cytology for nipple discharge has been shown to be of little value in most centres, and diagnostic major duct excision not only provides a diagnosis but is of therapeutic value[9].

Finally, there is considerable controversy as to whether mammary duct ectasia is the same condition as periductal mastitis. Periductal mastitis occurs at a younger age than duct ectasia[1]. Duct ectasia itself is so common as to be normal in women aged over 50 years, and women should not be given the impression they have diseased breasts just because they produce breast secretions or have multiple duct nipple discharge.

Cigarette smoking is clearly important in the aetiology of periductal mastitis[4,11], and influential in the natural history of this condition as women who develop non-lactating abscess and smoke have a much higher chance of developing mamillary fistula than those who do not smoke[11]. It is likely that smoking increases the anaerobic bacterial flora in breast ducts leading to early invasion when any necrosis occurs. Thus, logically, advice should be given that stopping cigarette smoking may help ameliorate the condition sooner. Women should be warned that, if they continue to smoke, they are also more likely to develop bilateral disease. Unfortunately, these important clinical messages were omitted from Mr Webb's article.

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Author's reply

Sir

I am most interested in the comments of Mr Bundred and wish to consider some of his criticisms.

The incidence of duct abnormality found at post-mortem examination is surprisingly high. The difficulty is to correlate this incidence with clinical findings. I endeavoured to suggest how this might be attempted by simple duct palpation. All studies of mammary duct ectasia–periductal mastitis (MDE–PDM) complex suffer from being unable reliably to identify the presence of tissue changes in the absence of complications.

The usual definitions of significant nipple discharge as being both spontaneous and persistent are restrictive; it is often intermittent. Two current definitions[1,2] accept that 'gentle expression' or 'a little provocation' are allowable to reveal the discharge and the duct orifices involved. I have never suggested more 'vigour' than this. Performing gentle nipple expression on all my patients, it is certainly not true that 70 per cent of premenopausal women can produce secretion. Indeed, natural physiological milky or creamy fluid is quite separate from the varied serosanguineous or opalescent, multicoloured secretions seen in MDE–PDM complex, and the cytology is also distinctive.

I have rarely found anxiety to be engendered by a gently expressed smear technique; in fact, quite the reverse. Women appreciate an explanation and an early report on the cytological findings.

I have been interested in and studied MDE–PDM since 1967 and, for example from my consulting practice, carry out around 1300 clinical breast examinations annually. Each year has been audited, and in 1995 there were 150 patients with a variety of mammary lesions in whom some form of clinical cytology was performed. Forty had nipple discharge; 25 premenopausal and perimenopausal (of whom 11 had spontaneous discharges) and 15 postmenopausal women, in whom seven were spontaneous. Two were associated with neoplasms. The results of this style of cytology have been reported[3]. The interesting finding in both groups is the variation in cell content related to macroscopic examination of MDE–PDM smears. Some are relatively acellular, others show marked atypia – particularly in regard to the foamy macrophages (colostrum cells) characteristic of duct ectasia. Epithelial hyperplasia short of neoplastic papillary formation is seen in both age groups. These features, together with other investigations, assist me in patient management.

The question of squamous metaplasia and developmental nipple inversion is an interesting aspect of subareolar sepsis; my view is supported by others[1].

Point 2: My experience is that, in a specific mastalgia situation, where there is clinical evidence of ductal thickening and a persistent area of breast tenderness and a period of simple expectant surveillance has failed, a short course of oral metronidazole (5–10 days) may help.

Point 4: My experience is as stated and is supported by views expressed from the Cardiff group[1].

Point 5: Despite adequate and careful excision of all grossly diseased tissue, together with the major ducts and with antibiotic therapy before and after surgery, experience has taught me to be cautious in forecasting cure. The mastectomies performed in Bristol were also done over 10 years ago.

Point 6: Mammography in an inflamed breast is not necessarily a rewarding investigation; it may be painful for the patient and the films are not diagnostic. I have never been successful in treating ectatic abscesses by aspiration and antibiotics. The situation requires adequate surgical drainage.

Point 7: Antibiosis before and after surgery will not necessarily avoid infective complications. I rely on adequate local excision, packing and secondary healing. The examples of gross abscess formation from both National Health Service and consulting practice have been followed for over 10 years. They remain quiescent and none has developed inflammation on the contralateral side.

Point 10: Gently expressible nipple discharge and smear cytology is a simple, swift, cost-effective addition to clinical examination[3]. It is our hope that epithelial neoplasia is revealed thereby and that epithelial instability will also be recognized, so that potential high-risk patients will not be lost to follow-up.

Point 11: Since the publication[4] in 1992, I have concentrated (as stated) on the question of smoking, MDE–PDM and infective complications. However, my advice to cease smoking has been uniformly ignored.

From palpation of mammary ducts, mammography and regular examinations, I am not able to confirm that duct ectasia is 'normal' over the age of 50 years. Most women have impalpable ducts and no other features. For 1995, from approximately 1300 breast reviews, only 38 women exhibited expressible or spontaneous nipple discharge with other features of the MDE–PDM complex, so perhaps the latter is a disease.

The arguments as to whether MDE is part of the same process as PDM are superbly marshalled by Hughes *et al.*[1], who concluded that perhaps three pathological processes may be operating.

The situation remains uncertain but fascinating, and the true position of bacterial infection in the process is obscure, so perhaps it is unwise to be too didactic.

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1 Hughes LE, Mansel RE, Webster DJT. Aberrations of normal development and evolution (ANDI): a new perspective on the pathogenesis and nomenclature of benign breast disorders. *Lancet* 1987; ii: 1316.
2 Horgan K. The management of nipple discharge. In: Mansell RE, ed. *Recent Developments in the Study of Benign Breast Disease.* Proceedings of the 4th International Benign Breast Symposium. April 1991. Carnforth, UK: Parthenon, 1992.
3 Dunn JM, Lucarotti ME, Wood SJ, Mumford A, Webb AJ. Exfoliative cytology in the diagnosis of breast disease. *Br J Surg* 1995; 82: 789–91.
4 Bundred NJ, Dover MS, Coley S, Morrison JM. Breast abscess and cigarette smoking. *Br J Surg* 1992; 79: 58–9.

'Gold standard'

Sir

You and your contributors say (*Br J Surg* 1996; 83: 279), quite rightly, get rid of the tired cliché 'gold standard'. I agree, although clichés are useful devices much exploited by those who wish to adopt a high ground either in science or morals.

Although I do not believe that all the triumphalism of the 'evidence-based medicine' movement is balanced or appropriate, the most accurate phrase to replace 'gold standard' is 'evidence-based standard'.

I must add that an evidence base is not confined to controlled clinical trials but also includes understandings of physiological mechanisms and the results from prospective clinical studies, which aim to find out where we are before embarking on the where we are going of a controlled clinical trial.

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Treatment and survival in 13 560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study

Sir

The paper by Mr Bramhall and colleagues (*Br J Surg* 1995; 82: 111–15) on pancreatic cancer in the West Midlands is one of the most realistic assessments of this disease. Of particular interest is the number of non-resected 5-year survivors; unfortunately they have not given the actual numbers, only the actuarial percentage. Can we have the actual number of 5-year survivors in each category?

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Authors' reply

Sir

We thank Dr Gudjonsson for his interest in our study and the data he requests are shown in the table. The database from which this information is obtained is constantly being updated as new information is received, so the numbers may not exactly match those used to calculate the survival analysis in the original paper.

	1957–1976		1977–1986	
Treatment	Total	No. surviving 5 years	Total	No. surviving 5 years
Resection	208	6	145	14
Bypass	2760	17	2010	17
Laparotomy alone	1552	3	825	3
Supportive care	3368	0	2710	0

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Polyposis: the Peutz–Jeghers syndrome

Sir

We were interested to read of the recommendation by the authors (*Br J Surg* 1995; 82: 1311–14) for mammography to be performed in women suffering from Peutz–Jeghers syndrome at ages 25, 30, 35, 38 years, then 2-yearly until 50 years, then yearly. While we compliment the authors on their intention to detect early associated diseases, we would like to point out that there is no evidence to show that screening for breast cancer using mammography, even in high-risk groups with a strong family history of breast cancer, is effective below the age of 35 years. At this age, the density of normal glandular tissue is likely to obscure any mammographic signs of early breast cancer. The recommendation for routine mammography at 25–35 years is clearly inappropriate. Regarding surveillance mammograms up to 50 years, there should be clear evidence of a significantly increased risk of breast cancer in these women for this to be justified. After 50 years, these women will be covered by the National Health Service Breast Screening Programme, and there is no recommendation currently for screening high-risk groups in this age group more frequently than the standard 3-yearly interval.

We suggest that the mammography recommendation of the Peutz–Jeghers Syndrome Data Sheet should be revised.

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Authors' reply

Sir

Thank you for the opportunity to respond to Messrs Parker and Michell. They have rightly focused on the area that caused us most difficulty when putting together our screening protocol for patients with Peutz–Jeghers syndrome. At the time, we took advice from a number of sources and these were distilled into the recommendations shown in our paper.

We acknowledge that screening for breast cancer is a controversial and vexed issue and will certainly take the comments of Messrs Parker and Michell into account when next revising our protocols, perhaps incorporating magnetic resonance imaging of the breast as technology improves.

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Endoscopic subtotal parathyroidectomy in patients with primary hyperparathyroidism

Sir

Since the first descriptions of successful parathyroidectomy for parathyroid tumour[1] in 1925 and subtotal parathyroidectomy for renal hyperparathyroidism[2] in 1960, few technical changes have occurred. In view of the natural benign history of minimally symptomatic primary hyperparathyroidism, controversy still exists about parathyroid surgery[3]. A new surgical approach has been attempted.

A 37-year-old man was admitted for investigation of severe pancreatitis; the patient had a familial history of hypercalcaemia and primary hyperparathyroidism. Apart from the previously resolved pancreatitis, there were no other signs or symptoms of hypercalcaemia. Computed tomography and magnetic resonance imaging of the abdomen revealed calcification of the entire pancreas, and endoscopic retrograde cholangiopancreatography showed a dilated pancreatic duct (14 mm in diameter), multiple pancreatoliths and no strictures. Echography of the gallbladder showed minimal sludge. Serum non-ionized calcium level was mildly raised (3·0 mmol/l; normal range 2·1–2·6 mmol/l) with a serum parathyroid hormone level of 10·2 (normal range 2·4–14·6 pmol/l). Echography of the neck did not show an adenoma, but a technetium-99m SESTAMIBI (Cardiolite; DuPont, Wilmington, Delaware, USA) scan showed four abnormal uptake foci consistent with primary hyperparathyroidism.

On 15 November 1995, the patient underwent laparoscopic cholecystectomy with cholangiography and laparoscopic longitudinal pancreaticojejunostomy with pancreatolith extraction. On 28 November 1995, he underwent endoscopic subtotal parathyroidectomy. Four 5-mm trocars were inserted under the platysma muscle, 1 cm above the clavicle and sternal notch. Carbon dioxide was insufflated to 15 mmHg to create a space above the strap muscles. Employing a 5-mm endoscopic scissor and dissector and a 5-mm 30° endoscope, the anterior and lateral borders of the trachea and thyroid were dissected. Biopsy specimens were obtained from four parathyroid glands. A left inferior thyroid nodule was found; a biopsy specimen was benign. Three and one-half glands were removed, and their blood supply was ligated with 5-mm titanium clips. The procedure took 5 h, and the patient had tachycardia (100–120 beats per min) and hypercarbia (end-tidal carbon dioxide level 41–45 mmol/l) necessitating hyperventilation. After operation he did well, with serum calcium level decreasing to normal (2·3 mmol/l). Subcutaneous emphysema was present from his eyelids to the scrotum and anteriorly on the thorax and abdomen, but it resolved on day 3 after surgery; the patient was discharged on day 4. He complained of hypersalivation for 3 days. A neck radiograph revealed carbon dioxide in the intermuscular planes.

This approach is feasible, cosmetically appealing, leaves the neck musculature intact and may benefit patients with primary hyperparathyroidism or parathyroid adenomas[4]. Vessels, nerves and nodes are highly magnified (× 15–20), which may result in less recurrent nerve damage. Also, this approach may facilitate exploring the mediastinum for ectopic parathyroid glands. Refinements in instrumentation should decrease operating time and limit subcutaneous emphysema and hypercarbia.

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1. Wellbourn R. *History of Endocrine Surgery.* New York: Praeger, 1990: 217–31.
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4. Strewler GJ. Indications for surgery in patients with minimally symptomatic primary hyperparathyroidism. *Surg Clin North Am* 1995; 75: 439–47.

British Journal of Surgery 1996, 83, 876–877

Book reviews

Pancreatic Cancer. Molecular and Clinical Advances

J. P. Neoptolemos and N. R. Lemoine (eds). 250 × 175 mm. Pp. 346. Illustrated. 1995. Oxford: Blackwell Science. £59.50.

I come across this book at a stand in the exhibition hall of a surgical meeting. I pick it up; an appetizing cover and title. Edited by Neoptolemos and Lemoine, foreword by Warshaw. I am tempted. I flip it over and read: '... In recent years, there have been many advances in the understanding of the molecular and genetic basis of the disease, with application of this knowledge to areas such as gene therapy. Divided into three sections, this book provides an up-to-date and comprehensive review of all aspects of pancreatic cancer research. The first section discusses pathophysiology of the disease at a molecular level. This is followed by a section on genetic advances and their clinical applications. The final section concentrates on current clinical practice...'. By now I am impressed and become more deeply so after glimpsing at Warshaw's foreword: '... The science displayed in this book provides an up-to-the-moment distillation of our understanding of how pancreatic cancer comes to be and its perhaps unique interactions with the surrounding matrix and supporting tissue...'. I desire this book badly and feel for my credit card but then, as usual, remember the towering pile of 'to be read' journals and books on my desk. With a deep sigh I return the book to the shelf.

Thus, when I receive this book from the Editors of the Journal I wonder whether it was an error in judgement not to purchase it before? I read its 25 succinct chapters, written by British ($n = 17$), German ($n = 17$), French ($n = 11$), Swedish ($n = 8$), Spanish ($n = 5$), Italian ($n = 3$) and North American ($n = 3$) authors. The unfortunate absence of 'summaries' or 'conclusions' was fortunate as it forced me to read all 17 cell biology and molecular genetics chapters. Obviously, being a 'simple clinician' and having no previous understanding or interest in basic pancreatic cancer research, I looked desperately for clinical relevance but did not find it. The chapters, however, are extensively and 'up-to-the-minute' (A.L. Warshaw, foreword) referenced, a great advantage for current and prospective researchers. Arriving at the clinical section I did not find much new. Same old unsolved controversies. While Beger *et al.* (chapter 18) are convinced that the Kausch–Whipple (every country has its own Whipple) procedure should include a 'regional' peripancreatic wide resection and 'peritoneal lavage', the Berne group (chapter 20) offer a more balanced view, suggesting that conventional and extended pancreatic resection should be compared in randomized studies. Similarly, while Beger and colleagues advocate and practise adjuvant radiochemotherapy, Bramball and Neoptolemos conclude chapter 23 with a statement that 'few surgeons routinely use adjuvant therapy at present but there is insufficient evidence to recommend a change in current practice'.

The overviews by Carter (indications for surgery) and Wagner, Friess and Buchler (conservative *versus* radical resection of the pancreas) offer refreshing and practical reading, but the conclusion in Hatfield's contribution on endoscopic management contains a mysterious statement: 'the use of expandable metal stents may also obviate the need for gastric outlet obstruction bypass surgery'. Do biliary stents treat gastric outlet obstruction or did the author develop a novel transduodenal stent?

It is a well written and edited book by well known experts. Would I have bought it? No, as it does not change or influence my current clinical practice. It certainly has a place in every library as a reference book for students, registrars preparing for higher examinations and researchers. Personally, however, I am sceptical about the role of such books in a changing world where all updated information is on the shelf (journals) or just a 'click' away.

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Hernia Repair: The Laparoscopic Approach

D. C. Dunn and D. Menzies. 277 × 222 mm. Pp. 138. Illustrated. 1995. Oxford: Blackwell Science. £55.

Many people have attempted laparoscopic inguinal hernia repair over the past few years, but the initial surge of enthusiasm has given way to the realization that this can be a technically demanding operation. If only this latest book by David Dunn and Donald Menzies had been available in the early days of the repair. The tome consists of ten chapters, encompassing all aspects of laparoscopic inguinal hernia repair, and is wonderfully illustrated in full colour with many photographs and corresponding diagrams to make interpretation easy. The authors have adopted a pragmatic style of prose, and interspersed the text with handy hints to ensure that this text remains a practical guide to laparoscopic repair. Both the transperitoneal technique and the preperitoneal procedure are dealt with in excellent detail, and I particularly enjoyed the chapter entitled 'Dealing with difficulties'.

This book is an essential acquisition for any surgical unit performing laparoscopic inguinal hernia repair and, although it is the trainee who will learn most by reading it, the experienced surgeon too may learn handy hints from its perusal. Without doubt this volume provides the essential information required to carry out laparoscopic inguinal hernia repair safely.

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Clinical Director's Handbook 1995/6

D. K. Hirst and R. V. Clements (eds). 256 × 190 mm. Pp. 249. Illustrated. 1995. Edinburgh: Churchill Livingstone. £75.

Are clinical directors born rather than made? Many practising clinicians, often senior and already extended with non-clinical work, have been selected as first-generation clinical directors with minimal or unhelpful training. They have had to learn on the job.

Hirst and Clements have produced the *Clinical Director's Handbook* for those clinicians, and particularly the next generation of directors. Written from the point of view of a clinician entering management, the essentials are all clearly and succinctly outlined. Issues, such as managing clinical activity, budgets and business planning, are all clearly described, and there is a good section on clinical audit and quality assurance. Helpful chapters on employing staff, the law, risk management and people management follow, to round off a very helpful and interesting book. The presentation is attractive. The volume contains all the essentials and, while some chapters have adequate references, other chapters have neither references nor suggestions for further reading which might be helpful for those who want to go into a subject in more detail.

This is a book for our time and it makes a concise, relevant and up-to-date contribution to the art of medical management. All clinical directors and those contemplating entering the field will be greatly encouraged by its straightforward jargon-free tone. It will be a valuable source of information and ideas and the publisher plans to bring out regular updated editions.

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Surgery of the Chest. 6th ed. Volumes 1 and 2

D. C. Sabiston Jr and F. C. Spencer (eds). 285 × 220 mm each. Pp. 2174. Illustrated. 1995. Philadelphia, Pennsylvania: W. B. Saunders. £195.

Since the first edition of *Surgery of the Chest* in the 1960s, it has remained a reference source for the apprentice cardiothoracic surgeon and inspiration for the mature one. This last edition is no exception. New chapters have been introduced to keep pace with rapidly evolving knowledge in research and clinical practice. For example, the chapter on fibrinolytic therapy in the management of acute myocardial infarction is a demonstration of the astute perception of the authors to the need of the practising surgeon. The same can be said for increased attention given in this edition to areas that are not strictly surgical but which are still highly relevant and educational, such as the chapter on dietary and pharmacological management of atherosclerosis. The two volumes cover completely the topics of thoracic and cardiac disorders. The authors have succeeded in presenting a comprehensive view of pathogenesis, pathological features, diagnosis and treatment. The factual information and the technical descriptions are presented in a precise, comprehensive and compact style that makes reading easy and pleasant. We live in an age of rapid change and continuously discover the complexities around us as in our clinical practice. These two volumes give us guidance and reassurance in sharing knowledge and understanding with some of the most illustrious names in the world of cardiothoracic surgery.

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Essential Surgical Practice. 3rd ed.

A. Cuschieri, G. R. Giles and A. R. Moossa (eds). 276 × 206 mm. Pp. 1656. Illustrated. 1995. Oxford: Butterworth–Heinemann. £75.

For a textbook of surgery to merit a third edition in a congested market place must reflect a degree of commercial success. Although aimed at postgraduate students, the breadth and depth of cover is impressive, and earlier editions are popular with undergraduates. This edition is expanded to include both adult and paediatric orthopaedics. The distribution of the 79 authors from central Europe to the west coast of America results in inevitable variation, although this is not intrusive. A substantial number of the clinical illustrations from colour transparencies have not reproduced well in monochrome. The relative merits of line drawings over clincial photographs in depicting operations is nowhere better illustrated than in the chapter on surgery of the face. However, the reconstructed faces will engender a sense of proportion in the student unfamiliar with the realities of major head and neck surgery. It is not difficult in a book of this size to find errors, for example inverted radiographs. However, these are infrequent, although one would expect that a chapter on colorectal surgery would spell Eisenhammer and Parks correctly. The handling of references is inconsistent, with an excessive bibliography of 47 references for critical care whereas colorectal surgery is completely unreferenced. These criticisms, however, are of a relatively minor nature and the overall impression is of a comprehensive textbook which achieves its objective and will maintain its popularity.

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Transplantation Immunology

F. H. Bach and H. Auchinloss Jr (eds). 260 × 193 mm. Pp. 409. Illustrated. 1995. New York: Wiley–Liss. £60.

To indicate that one has enjoyed reading a book on transplant immunology is likely to induce the incredulity epitope in surgical colleagues. However, the strength of this book is that considerable care has been taken not to assume that the reader has a detailed knowledge of basic immunology. It is, therefore, possible by reading the first few chapters to understand histocompatibility, and the ever more complex interactions and signalling processes involved in lymphocyte functions. Following this solid start the editors have bolted on a selection of chapters which, while not totally comprehensive, cover most of the 'hot topics' in transplantation. There is an excellent section on various aspects of tolerance, with individual chapters on xenotransplantation, and transplantation of the bone marrow and the pancreas. There is also a well written update on new, small molecule, immunosuppressive agents. It would be worth acquiring the book for the final chapter alone – 'Molecular biology for the clinician'. If you do not know what is in a TATA box or a cDNA library, this is the place to find out. The book will be stimulating reading for clinicians involved in transplantation and an excellent reference text for the laboratory scientist.

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British Journal of Surgery 1996, 83, 878

Notices and announcements

12–15 June 1996

International Association of Pancreatology

Mannheim, Germany

Information: Mr A. L. Warshaw, IAP Secretary, Massachusetts General Hospital, 15 Parkman Street, WAC 336, Boston, Massachusetts 02114, USA

16–22 June 1996

38th Annual World Congress of the International College of Angiology

Köln, Germany

Information: D. M. Rossignol, Executive Director, International College of Angiology, 5 Daremy Court, Nesconset, New York 11767, USA

23–26 June 1996

4th International Congress of the European Association for Endoscopic Surgery

Trondheim, Norway

Information: Congress–Conference A/S, PO Box 7609 Skillebekk, N-0205 Oslo, Norway

26–29 June 1996

CAR'96 – Computer Assisted Radiology 10th International Symposium and Exhibition

Paris, France

Information: Professor H. U. Lemke, Technical University Berlin, Institute for Technical Informatics, Sekr. CG FR 3-3, Franklinstrasse 28–29, D-10587 Berlin, Germany

27–28 June 1996

Surgical Research Society

Birmingham, UK

Information: Ms L. Hopwood, University Department of Surgery, Royal United Hospital, Bath B15 2TH, UK

29 June–3 July 1996

7th Annual Training Course for Clinicians: Practical Nutritional Support

Southampton, UK

Information: Mr B. Moran, Institute of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton SO16 7PX, UK

5–6 July 1996

Current Status of Surgical and Interventional Procedures for the Management of Aortic Aneurysm, Reno-Vascular Disease and Carotid Stenosis

Stratford-upon-Avon, UK

Information: Mrs L. de Cossart, Consultant Surgeon, Countess of Chester Hospital, Liverpool Road, Chester CH2 1UL, UK, or Dr J. Dyet, Consultant Radiologist, Hull Royal Infirmary, Anlaby Road, Hull HU3 3KZ, UK

7–9 July 1996

Joint Meeting of British Oncological Association in association with Royal College of Radiologists, British Institute of Radiology and British Society for Cell Biology

Cardiff, UK

Information: Meeting Secretariat, BOA 1996, 4 Cavendish Square, London W1M 0BX, UK

8–10 July 1996

Tripartite meeting of the Association of Coloproctology of Great Britain and Ireland, Section of Coloproctology of the Royal Society of Medicine, American Society of Colon and Rectal Surgeons, Section of Colon and Rectal Surgery of the Royal Australasian College of Surgeons, Colorectal Surgical Society of Australia

London, UK

Information: Confrex, Conference Secretariat, 145 Islingword Road, Brighton, Sussex BN2 2SH, UK

8–10 July 1996

Association of Coloproctology Tripartite Meeting

London, UK

Information: Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–19 July 1996

Advanced Course in Surgery

Hong Kong

Information: Course Secretary, Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, Hong Kong

11–12 July 1996

British Association of Surgical Oncology Summer Scientific Meeting

Oxford, UK

Information: Mrs V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 July 1996

Hong Kong Surgical Forum – Summer 1996

Hong Kong

Information: Forum Secretary, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

4–8 September 1996

International Congress of Phlebology

Corfu, Greece

Information: Professor P. Balas, 4 Hiraclitou Street, Athens 10673, Greece

6–8 September 1996

6th National Conference of the Indian Association of Surgical Gastroenterology

New Delhi, India

Information: Professor T. K. Chattopadhyay, Secretary, IASG, Department of Surgery, All India Institute of Medical Sciences, New Delhi 110029, India

8–12 September 1996

Annual Meeting and Postgraduate Course of the Cardiovascular and Interventional Radiological Society of Europe

Funchal, Madeira

Information: CIRSE 96, Pilatusstrasse 14, CH-8032 Zurich, Switzerland

9–11 September 1996

Basic Surgical Skills Workshop

Liverpool, UK

Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

11 September 1996

European Board of Surgery (Qualification in Vascular Surgery Assessments)

Venicer, Italy

Information: J. Buth, Secretary of the Division of Vascular Surgery and the European Board of Vascular Surgery, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, The Netherlands

18–19 September 1996

Fundamental Techniques of Plastic Surgery

Swansea, UK

Information: British Association of Plastic Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–20 September 1996

Society for Minimally Invasive Therapy 8th International Meeting

Milan, Italy

Information: G. Carminati, Istituto di Urologia, Universita degli Studi, Via della Commenda 15, 20122 Milan, Italy

19–21 September 1996

International Meeting on Inflammatory Bowel Disease

Capri, Italy

Information: Professor R. Caprilli, Cattedra di Gastroenterologia, Università de L'Aquila, Via S. Sisto 22E, 67100 L'Aquila, Italy

Instructions to authors

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Following final approval of articles, authors are asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Particular attention should be taken to ensure that any articles submitted adhere **exactly** to Journal style in all respects. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; 296: 401–5 or the *Annals of Internal Medicine* 1988; 108: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the brief name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary of no more than 150 words on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation. **Randomized controlled trials** should be clearly identified as such in the title and summary.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

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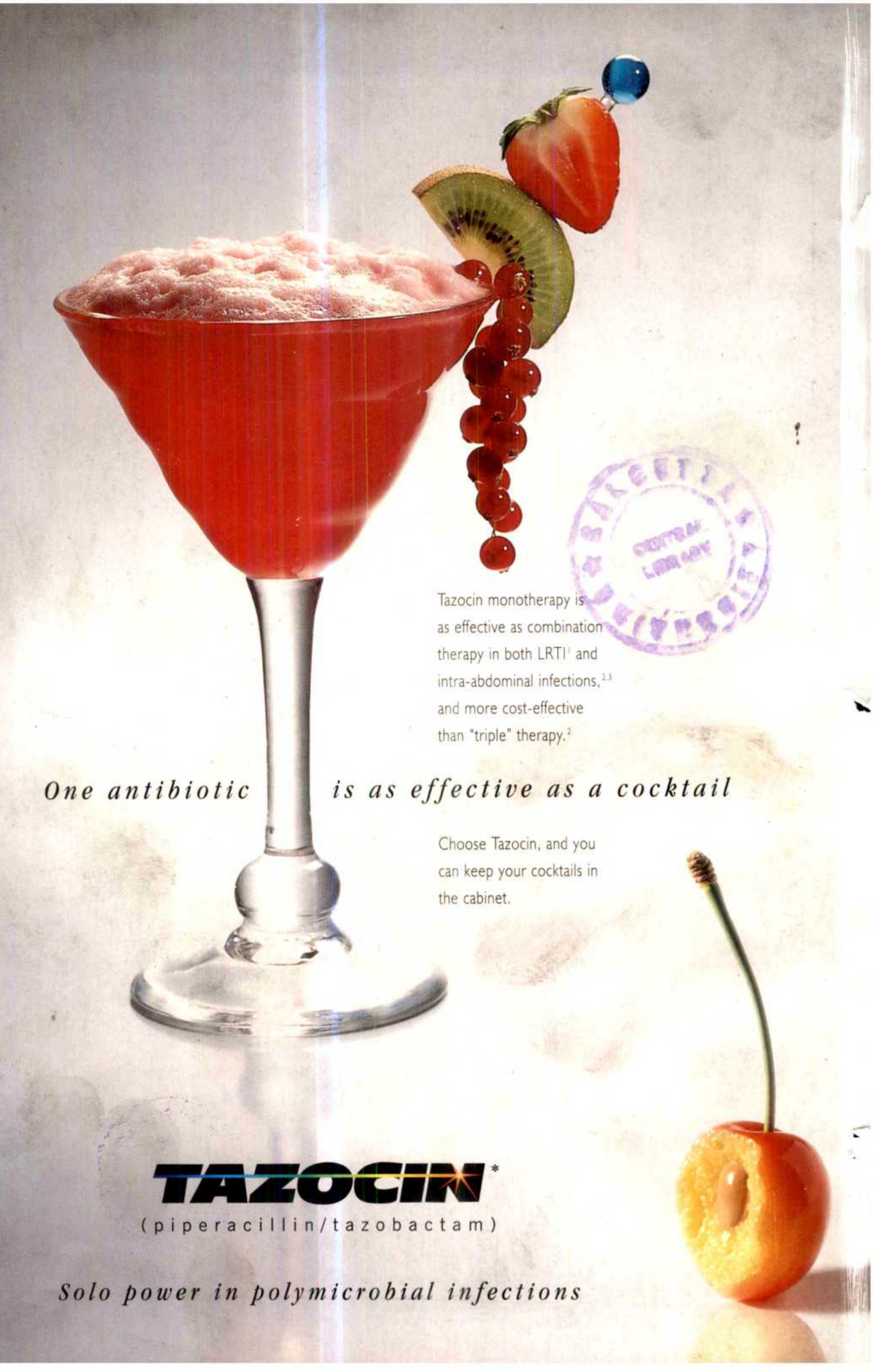

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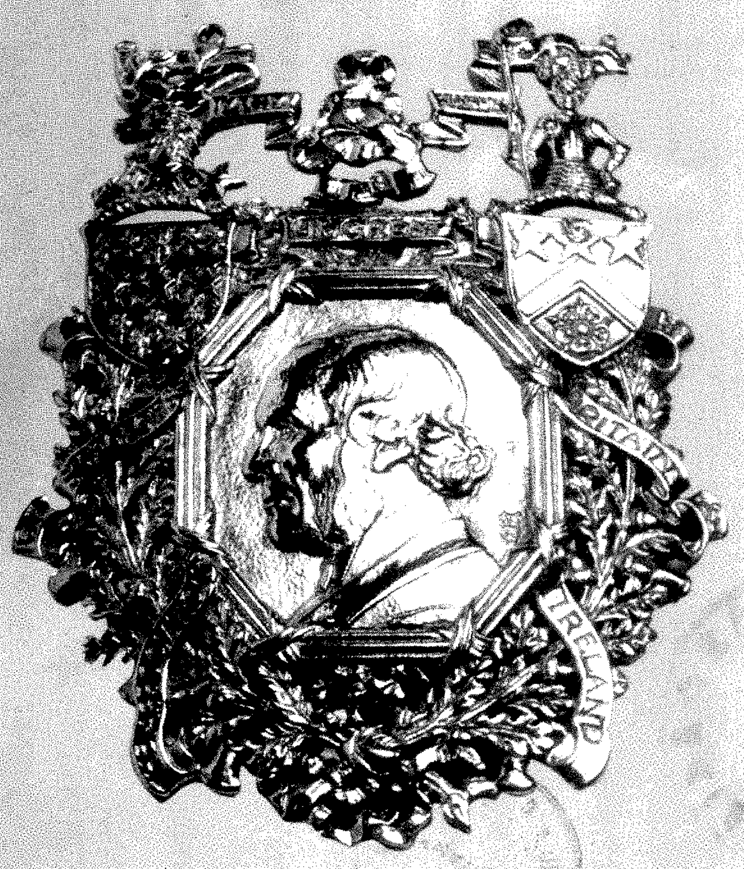

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ISSN 1355-7688

Typeset by Unicus Graphics Ltd
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The British

Journal of Surgery

Volume 83 Supplement 1 June 1996

Association of Surgeons of Great Britain and Ireland

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This year the Journal is breaking new ground in the special relationship by publishing this supplement, which contains the abstracts for the 1996 Association Meeting. These abstracts show the considerable strength and depth of surgical research that is to be found in Great Britain and Ireland today. It is expected not only that the supplement will provide easy access to data during the Glasgow meeting, but also that it will have a shelf-life for purposes of future reference that is commensurate with the importance of its contents. The editors hope you will find the format attractive; on their behalf I wish all participants an enjoyable congress in Glasgow.

John Murie
Review Editor, BJS

LGI 001

Laparoscopic-assisted resections for Crohn's disease and recurrent Crohn's disease

N.C. Gallegos and R.W. Motson *Colchester General Hospital, Colchester, Essex*

Fourteen patients (median age 32 years) with either radiologically suspected ileal-caecal Crohn's disease (8) or an anastomotic recurrence following previous limited right hemicolectomy (6) underwent laparoscopically assisted surgery. Four patients had a palpable mass preoperatively but none had a demonstrable fistula. Abdominal ports were established, and after confirming the solitary site of disease, the affected ileum and colon were mobilized by laparascopic dissection. The bowel was then exteriorized through a limited incision (mean length 6 cm), the affected segment resected (mean length, 22 cm) and an extracoporeal anastomosis performed.

Inadvertent injury to intra-abdominal structures did not occur, there were no deaths and no patient suffered an anastomotic dehiscence. Two patients required conversion to a formal laparotomy; one because of the complexity of their current disease, the other because of the unexpected extent of disease affecting the right colon. In one patient strictureplasty was sufficient treatment. For the 12 patients completed laparoscopically the median operating time was 120 minutes and the median hospital stay 6 days.

Laparascopically assisted surgery for Crohn's disease can be carried out safely in selected patients. Its use may be seen as a way of minimising surgical trauma in patients predisposed to repeated operation.

LGI 002

Prospective controlled trial of duplicated (J) versus quadruplicated (W) ileal reservoirs for ulcerative colitis

A.S. Miller, M.E.R. Williamson, W.G. Lewis, P.M. Sagar, P.J. Holdsworth and D. Johnston *Academic Unit of Surgery and Centre for Digestive Diseases, General Infirmary, Leeds*

A prospective randomised controlled trial was conducted to find out what influence the design and size of the pelvic reservoir had on functional outcome one year after operation. Sixty patients received either a duplicated (J) or a quadruplicated (W) reservoir, each of which was constructed either with 30 cm or with 40 cm of terminal ileum. Each patient underwent laboratory tests of anorectal function before and one year after operation.

Reservoir design	J30	J40	W30	W40
Number	13	15	15	14
Age (years)	32	32	33	33
Bowel frequency per 24 h	5	6	5	4
Max tolerated volume (ml air)	220	250	250	310
Compliance (ml air/cm water)	6·7	7·5	7·6	8·7
Leakage of mucus	2	2	3	1
Failure	0	2	0	0

All values are median. P = N.S.

Both the capacity and compliance of the W40 reservoirs were greater than those of the other designs, but the differences were not significant. These findings provide support for the use of a relatively small (30 cm), duplicated (J) ileal reservoir, which is simple to construct with linear stapling instruments.

LGI 003

Restorative proctocolectomy in patients on systemic steroids

S.E. Wakefield and A.J. Shorthouse *Royal Hallamshire Hospital, Sheffield S10 2JF*

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the treatment of choice for most patients with ulcerative colitis requiring surgery. The role of high-dose steroids in reduced healing potential and increased infection-related problems is well known. This had led many surgeons to opt for a 2- or 3-stage procedure in patients on steroids. We report our experience with IPAA in patients on systemic steroids at the time of operation. Our policy has always been that IPAA is performed at operation if the patient is clinically well and has normal haemoglobin and albumin values. If not a preliminary colectomy with end ileostomy is performed.

A total of 64 consecutive patients undergoing ileal pouch surgery were studied (males 40, mean age 35·4 years, ulcerative colitis 60). At the time of surgery 31 patients were on systemic steroids (average daily steroid requirement 22·5 mg of Prednisolone or intravenous equivalent). In addition 11 patients on steroids were also on Azothiaprine.

No difference between patients on or off steroids at the time of surgery was found with respect to radiological leaks at the IPAA (2 vs 3; $P = 0{\cdot}694$), pelvic sepsis (2 vs 2; $P = 0{\cdot}590$), fistula formation (1 vs 1; $P = 0{\cdot}964$) or postoperative bleeding (1 vs 1; $P = 0{\cdot}982$). The incidence and time to first episode of pouchitis was similar in both groups ($P = 0{\cdot}673$) as was the pouch function score at 3, 6, 12, 18, 24 and 36 months.

Pouch construction in patients on systemic steroids is safe providing their clinical condition is good and haemoglobin and albumin levels are within normal ranges.

LGI 004

Re-operation following restorative proctocolectomy

S. Korsgen and M.R.B. Keighley *University Department of Surgery, Queen Elizabeth Hospital, Birmingham*

We have analysed re-operations following restorative proctocolectomy and ileopouch anal anastomosis (IPAA) in 180 patients between 1983 and 1993 (familial adenomatous polyposis (FAP; n = 26), ulcerative colitis (UC; n = 154)).

There were 7 re-operations (7 patients) in the FAP group (27 per cent); excision of a desmoid (1), laparotomies for small bowel obstruction (n = 5: 1 · resection), secondary loop ileostomies (4) and dilatation of an ileoanal stenosis (1).

There were 121 re-operations (60 patients) in the UC group (39 per cent); these included early pouch excisions for pouch infarction (5), laparotomy for small bowel obstruction (n = 10: 3 resections), operations for pouch related fistulas (25 in 19 patients), anal or pelvic operations to control sepsis (23 in 14 patients), secondary loop ileostomy (36 in 28 patients), for sepsis (13), bleeding (2), pouch fistula (11), chronic pouchitis (2), poor pouch function (6) and small bowel obstruction (2), dilatations of an ileoanal stenosis (30 in 23 patients) and 6 miscellaneous operations. 62 re-operations were recorded in 27 patients in the first 50 cases (54 per cent) compared with 58 procedures in 23 patients in the last 104 patients (32 per cent).

These results indicate that at least a third of UC patients will require re-operations after IPAA.

LGI 005

Long-term results of ileal pouch-anal anastomosis (IPAA) in patients with Crohn's disease

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The aim of this study was to determine outcome of patients with Crohn's disease who have undergone IPAA.

Thirty-seven patients (20 men) were studied. Each had undergone mucosectomy with hand-sewn IPAA (J pouch $n = 35$, S pouch $n = 1$, W pouch $n = 1$). Histological examination of the resected specimen showed features of ulcerative colitis ($n = 22$), indeterminate colitis ($n = 9$) and Crohn's disease ($n = 6$). The stoma was closed in all patients.

Eleven of 37 patients have developed complex fistulas [pouch-cutaneous ($n = 6$), pouch-vaginal ($n = 4$) or pouch-vesical ($n = 1$)]. Crohn's disease has recurred in the pouch ($n = 20$), anal canal ($n = 4$), pouch and anal canal ($n = 10$) and elsewhere ($n = 3$). After 10 years (range 3–14), the pouch remains *in situ* in 20 patients, *in situ* but defunctioned in 7 patients and excised in 10 patients (failure rate = 45 per cent).

Inadvertent IPAA for Crohn's disease is associated with a high rate of failure (45 per cent) but an acceptable long-term functional result if the pouch can be kept *in situ*.

LGI 006

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the treatment of patients with distal procto-colitis

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Recently, it has been postulated that patients with inflammatory bowel disease (IBD) have an altered status of natural cytotoxicity, in particular natural killer (NK) and lymphokine-activated killer (LAK) cell activities. We have shown previously that the essential fatty acids (EFAs), EPA and DHA, specifically inhibit natural cytotoxicity. The aim of this study, therefore, was to evaluate the effect of these EFAs on distal proctocolitis. Each patient received either fish oil extract (EPA 3·2 g, DHA 2·4 g) ($n = 9$) or placebo ($n = 9$) daily in a double-blind manner for six months. Monthly assessment included: (1) disease activity using clinical and sigmoidoscopic scores, and (2) monitoring the circulating levels and activities of NK and LAK cells, using FACS analysis (CD16$^+$, CD56$^+$ surface markers for NK and LAK cells) and *in vitro* 51 chromium release assay (K562), respectively. In the treatment group, there was improvement in the disease activity scores (8, 3–10), compared with pretreatment evaluation (16, 7–25) [median, range]. Analysis between the two groups showed significant reduction in the circulating numbers of CD16$^+$ (0·22 × 10^9 cell/l) [median change] and CD56$^+$ (0·12 × 10^9 cell/l), compared with placebo group (0·34 × 10^9 and 0·22 × 10^9 cell/l, respectively). In addition, EFA supplementation for six months induced reduction in the cytotoxic activity of NK cells, compared with the placebo group (34 vs 81·3 LU30).

This pilot study has demonstrated that EPA and DHA can suppress natural cytotoxicity and may reduce disease activity in patients with IBD.

[FACS: fluorescent activated cell sorter; LU30: lytic units, number of effector cells required to kill 30 per cent of target cells; $P < 0·05$, Wilcoxon and Mann–Whitney U tests].

LGI 007

How safe is the double-stapled ileoanal reservoir in ulcerative colitis?

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The malignant potential of the retained anorectal mucosa after restorative proctocolectomy (RPC) with double-stapled ileoanal reservoir (DSIAR) without mucosectomy is an aspect of this procedure which causes some concern.

Aim: To study the incidence and the type of dysplasia in the retained anorectal mucosa at the time of the intitial surgery as well as in the post-operative period.

Patients and methods: The results of the histology of 109 patients who underwent surgery for mucosal ulcerative colitis (MUC) with DSIAR both at the time of the intitial surgery as well as during subsequent follow-up were reviewed.

Results: Only one patient out of 109 was found to have dysplasia in the distal rectal doughnut at the time of the intitial surgery. Over the mean follow-up period of 2·6 (1–6) years, a total of 186 follow-up biopsies (mean of 1·7 per patient) were reviewed. There was no dysplasia in any of the follow-up biopsies including the biopsies from the one patient who had low-grade dysplasia in the doughnut at the time of surgery.

Conclusions: The incidence of dysplasia in our series was low; no carcinoma was identified. RPC with DSIAR for patients with MUC is a safe option in terms of the malignant change in the retained mucosa. Further long-term follow-up studies will need to be conducted to better quantify this risk.

LGI 008

Stapled laparascopic rectopexy for rectal prolapse

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Procedures for treating rectal prolapse (procidentia) may constitute some of the best applications for colorectal laparoscopic techniques as there are no problems with specimen retrieval or tumour seeding. We report our results of forty-eight consecutive stapled laparascopic rectopexies.

The operation is performed with the patient in the Lloyd-Davis position using four ports. The rectum is carefully mobilised down to the pelvic floor and a strip of polypropylene mesh measuring approximately 10 × 6 cm is introduced into the abdomen. The LapTac anchoring device (Surgin, US) is then introduced into the right iliac fossa port, and the mesh is initially fixed to the sacrococcygeal area. After fixation of the mesh, the rectum is held under light tension using the laparascopic Babcock forceps and the mesh is sutured to the serosa of the rectum. The peritoneal edges are approximated and stapled using an Endo hernia stapler.

The median age was 71 years (52–89) with a male:female ratio of 2:46. One procedure was converted due to ventilatory difficulties. Mean operative time was 95 minutes (50–190). The mean hospital stay was 5 days (4–15). Complications were trocar-site hernia ($n = 1$), extraperitoneal haematoma ($n = 1$), and urinary tract infection with retention ($n = 1$). There were no deaths.

Our preliminary experience with laparoscopic rectopexy is encouraging, with early mobilisation and discharge being a marked feature. Although follow-up is short, the functional results have been excellent. In conclusion, laparascopic abdominal rectopexy is a safe and effective technique in the management of rectal prolapse.

LGI 009

The learning curve of laparoscopic colorectal surgery – a single surgeon's experience of 115 cases over 3 years

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The role of the laparascopic technique in colorectal surgery is controversial because of concerns over feasibility, cost, benefit, and cancer recurrence. There have only been a few reported series, and the results have varied considerably.

Over a 3-year period, 115 laparoscopic colorectal procedures were performed (resection rectopexy 47, loop colostomy 25, subtotal colectomy 15, anterior resection 11, ileocaecal resection 5, right hemicolectomy 8 and rectal excision 5). All but two were for benign indications (rectal prolapse, slow transit constipation, adenoma, Crohn's disease, volvulus and angiodysplasia). In the first 50 cases, there were 7 (14 per cent) conversions and there were 9 (18 per cent) complications: 3 ureteric injuries (one required ureteric reimplantation), 2 small bowel obstruction, 1 intra-abdominal sepsis (negative laparotomy), 1 pancreatitis, 1 pyelonephritis, and 1 port site hernia. In the second half of the series, there was 1 (2 per cent) conversion and 2 (3 per cent) complications: anastamotic stricture, and haemorrhage requiring transfusion. Long-term results were identical to those of open surgery. Operative and recovery times (median/range) are shown below:

	Operation time (mins)	Time to diet (days)	Postop stay (days)	Return to normal activity (days)
Rectopexy	180 (165–300)	2 (1–100)	4 (3–110)	14 (7–110)
Subtotal colectomy	190 (170–390)	2 (1–3)	4 (3–7)	10 (7–21)
Miscellaneous	100 (90–240)	3 (2–7)	4 (4–11)	14 (12–28)

In conclusion, laparoscopic colon resection results in a more rapid postoperative recovery, while operation time is modestly increased. Major complications and conversion to open surgery were related to the learning curve.

LGI 010

Hartmann's procedure – outdated or not?

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Increasing tendency towards resection and primary anastomosis, even in the presence of obstruction or peritonitis, leads us to believe that Hartmann's may be an outdated procedure. A retrospective audit of 71 patients undergoing Hartmann's procedure between 1990 and 1995 was made at our hospital.

		Benign (52 per cent)		Malignant (48 per cent)	
Mean age		65 years (range 30–84 years).		68 years (range 42–94 years)	
Presenting pathology					
Diverticular	Non-faecal peritonitis	16	Adeno Ca	Dukes A	1
	Faecal peritonitis	7		B	13
	obstruction	7		C	17
	bleeding	1			
	vesico-colic fistula	1	Ovarian Ca		3
Others		5			
Percentage reversed		65 per cent		32·3 per cent	
Percentage awaiting reversal		11 per cent		6 per cent	

Thirty-day mortality was 3 patients (8 per cent) with benign, and 3 patients (8·8 per cent) with malignant disease, relatively low when compared with other studies. Morbidity totalled 28 per cent for all procedures. Median time before reanastomosis was 5·5 months. An attempted reanastomosis failed in two patients (2·8 per cent). A consultant was present in 26·7 per cent of cases, and 54·3 per cent of reversals. It is a safe procedure and NCEPOD will be gratified to know that only 12 per cent were performed after midnight.

Vascular 001

Cross-matching blood for elective aneurysm repair: a thing of the past?

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Blood transfusion in surgery has hidden dangers, may have limited availability and is expensive. Using autologous blood may avoid such problems. We have evaluated autologous blood transfusion in patients undergoing abdominal aortic aneurysm (AAA) repair.

Three units of blood were donated 14 and 7 days before operation, and immediately prior to surgery. At surgery, blood was salvaged using a Cell Saver III Plus autotransfusion system. Autologous blood was reinfused intra- and post-operatively. Serial haemoglobin (Hb) levels were measured before and after surgery.

Twenty-four of 71 patients (34 per cent) were not predonated according to protocol criteria. Forty-seven patients were predonated, but in two autologous blood passed its expiry date due to operational postponement. Median (interquartile range) intraoperative blood salvage was 515 (368–870) ml. Six patients were transfused with bank blood in breach of protocol and six others were transfused according to clinical need. Excluding protocol violations and postponements, 33 of 39 patients (85 per cent) required no bank blood.

Autologous predonation and intraoperative blood salvage reduces or prevents the need for bank blood in AAA repair. This has led to a new policy of avoiding cross-matching for AAA repair in predonated patients.

Vascular 002

Use of base deficit as a predictor of outcome following abdominal aortic surgery

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It would be very helpful if patients destined to do badly with aortic surgery could be identified preoperatively, particularly when they present as an emergency. A significant contributing factor to perioperative deaths is inadequate tissue perfusion or dysoxia. Measurement of base deficit (BD) on arterial blood is a rapid, precise and discriminating marker of tissue oxygenation. Base deficit is as consistent as gastric intramural pH, a known predictor of dysoxia, which also correlates with morbidity and mortality in patients following major surgery.

A retrospective review of a hundred patients and a prospective study of twenty patients has correlated values of base deficit and oxygen saturation with outcome following abdominal aortic surgery. The data for survivors and non-survivors have been examined to assess the predictive potential.

The mean base deficit of survivors was −4·04 ± 2·7 mmol/l while the mean BD of those who died was −11·8 ± 5·81 mmol/l ($P < 0·001$). Arterial oxygen saturation was adequate in both groups, 96·38 per cent and 96·6 per cent respectively. Increasing age significantly correlated with death and the product of age and BD proved to be a useful predictive index (−280 ± 199 for survivors and −860 ± 430 for deaths). The results from the retrospective study have been confirmed in the patients studied prospectively.

Base deficit as a single marker proved to be significant as a predictor of outcome following abdominal aortic aneurysm surgery. It may also prove to be the most rapid and convenient indicator of viability in patients considered for emergency aortic surgery.

Vascular 003

Is endoluminal repair of abdominal aortic aneurysms a durable procedure?

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Endoluminal AAA repair involves the insertion of an intraluminal prosthetic graft via the femoral or iliac arteries, with the aim of excluding the aneurysm sac from the circulation. Although reports of initial experience from several centres have demonstrated the feasibility of this technique, the long-term outcome remains uncertain.

Over a 19-month period from March 1994 to September 1995, we have attempted endoluminal AAA repair in 19 patients (18 M: 1 F; median age 73·5 years; median AAA diameter 5·6 cm). An aortoaortic (tube) graft repair was attempted in 7 patients, a tapered aortoiliac reconstruction in 10 patients, and a bifurcated graft in 2 patients. There were 3 initial failures requiring conversion to open repair. The median operative time was 195 min (range 95–270), median blood loss was 1200 ml (range 500–3500) and the median hospital stay was 7 days (range 4–21). Complications included 1 early death, 1 patient with reversible ATN, 1 patient who required prolonged ventilation and 2 patients with buttock claudication. Follow-up with Duplex and contrast-enhanced CT scans demonstrated graft migration in 1 patient requiring conversion and 3 perigraft leaks (2 proximal and 1 distal). One further distal leak developed at 12 months after operation. Two patients underwent late conversions, one due to aneurysm expansion as a result of a persistent proximal perigraft leak (6 months after operation) and the other due to a new distal leak detected at one year. The latter patient had developed dilatation of the distal neck and aneurysmal changes in the left common iliac artery. Histological examination of the explanted intraluminal graft in both patients did not demonstrate any endothelial cover or healing pannus in the graft or at the stent sites.

We conclude that endoluminal AAA repair is feasible but not free of significant complications. However, of greater concern is the late graft failure as a result of dilatation of the distal neck and the lack of incorporation of the intraluminal graft at the stent sites. Therefore we recommend careful long-term evaluation of this technique prior to its widespread use.

Vascular 004

A six-month prospective study of patients presenting with abdominal aortic aneurysm to a single health region

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Data were collected prospectively on all patients presenting with AAA to one teaching hospital (TH) and in district general hospitals (DGH) covering a population of approximately 2·5 million. One hundred and forty-eight patients presented, M:F = 6:1. The median age of patients having operation for ruptured aneurysm was 68 years, those with ruptured aneurysm not having an operation was 74 years (ns). The age of patients presenting with elective aneurysm was 72 years.

Two patients presented with acute non-ruptured aneurysms. Forty-four patients (31 per cent) presented with rupture. Twenty-three of these patients died (52 per cent). Of the 35 having an operation 13 (37 per cent) died. Of 19 patients having an operation for a ruptured aneurysm carried out in the TH, three died compared with 10 of 16 in DGHs ($P < 0·02$ chi square test). Analysis of referral sources for patients having an operation for ruptured AAA revealed that 8 of 19 TH patients were transferred from other hospitals, the diagnosis having already been made. This compares with only 1 of 16 DGH patients ($P < 0·05$). One patient died whilst being transferred to the TH.

One hundred and two patients presented electively and an operation was performed in 50. There was no significant difference in mortality between those operated upon in a teaching and those in a DGH (three patients died). Thirty-two of 52 patients not having an operation had small aneurysms and were entered into a surveillance programme. The remainder were either unfit or too old for operation.

The reduced mortality of patients having an operation for a ruptured aortic aneurysm in a TH can largely be explained by a referral pattern which results in selection of fittest patients for operation. Only half of those patients with an AAA presenting electively need a plan for an operation. The majority of the remainder have small aneurysms which need surveillance. This has cost and resource implications.

Vascular 005

Cost-effectiveness in treating ruptured abdominal aortic aneurysm

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Mortality rates for patients undergoing surgery for ruptured abdominal aortic aneurysm (RAAA) remain high. The high cost of providing care for these patients mandates that proposed treatment protocols be evaluated for their cost-effectiveness. This study assessed costs related to outcome in different groups of patients with RAAA. From July 1987 to December 1993, 140 patients underwent emergency surgery for RAAA. Complete data on preoperative haemodynamic status, blood transfusion requirements, intensive care unit (ICU) stay and other hospital costs, was available on 102 patients. Eighty-five males (mean age 71·6 ± 6) and 17 females (mean age 77·2 ± 6) underwent surgery. Known risk factors including age (< or > 70 years), shock on admission (blood pressure [BP] < or > 90 mmHg), sex and acute renal failure were analysed. For the purpose of comparison, costs (IR£) were assessed by the ESRI based on 1992 prices.

Sex	Age (yrs)	BP mmHg	RAAA *n*	Survivors *n*	% survival	Cost/ RAAA (IR£)	Cost/ survivor (IR£)
Male	<70	>90	25	18	72	5650±3666	7847
Male	<70	<90	8	3	37·5	6350±4234	16932
Male	>70	>90	40	28	70	6122±2732	8745
Male	>70	<90	12	5	42	7358±2817	17659
Female	>70	>90	10	2	20	5432	27182†
Female	>70	<90	7	3	43	20224±8075	47189*

(Mean ± sd) *$P < 0{\cdot}05$ *v* Male > 70 years; BP < 90mmHg; †$P < 0{\cdot}05$ *v* Male > 70; BP > 90mmHg (Student's *t*-test)

The overall survival rate was 58 per cent (63 per cent male; 29 per cent female; $P < 0{\cdot}05$ chi square test). In addition to having a significantly worse outcome than males, female patients with RAAA also had longer hospital and ICU stays and this was reflected in significantly greater expenditure. Similarly male patients >70 years presenting with haemodynamic instability had significantly longer hospital and ICU stays than younger male patients. The overall average cost per RAAA survivor (IR£13 354) in this series is not prohibitive and the greater cost should not discourage aggressive intervention in high-risk groups.

Vascular 006

What is the major cause of death from aortic aneurysm surgery? Results of 4-year prospective audit of 222 cases

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In order to decrease the mortality associated with infrarenal abdominal aortic aneurysms (AAA), some authorities have strongly recommended a full work-up of the cardiac system. We audited our aneurysm results from August 1991 to July 1992 to ascertain the causes of death.

Category	Number	Deaths	Cause
Elective	105	4	MOF, pneumonia, CVA, aspiration
Urgent	76	7	MOF × 3, ischaemic colitis, paraplegia PE, respiratory failure
Emergency	40	14	MOF × 4, MI × 3, IsC × 2, bleeding × 3, CVA, reperfusion
All	222	25	

MOF = multiple organ failure, MI = myocardial infarction, CVA = cerebrovascular accident, IsC = ischaemic colon.

Modern anaesthetic techniques allied to improvements in surgical technique and postoperative care have annulled the importance previously placed upon ischaemic heart disease. The major cause of death in this consecutive series of AAA repair is colonic ischaemia resulting in 11 of the 25 (44 per cent) deaths. Multiple organ failure is related to translocation of bacteria from the colon during periods of splanchnic ischaemia. Methods to identify patients at high risk of splanchnic ischaemia and techniques to improve splanchnic blood flow may be the most important way of decreasing mortality.

Vascular 007

The radiological and surgical consequences of a femoropopliteal graft surveillance programme

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Introduction: Long-term graft patency can be improved by a surveillance programme for femorodistal grafts (vein and synthetic conduits). The purpose of this study was to examine the radiological and surgical consequences and cost of providing this service.
Methods: Eighty-one patients had femorodistal bypass grafts in a 12-month period. Forty-three patients had synthetic grafts and 38 had vein grafts (26 femoropopliteal and 12 femorocrural grafts). A record was kept of all the consumables and an average cost for each type of radiological procedure could then be calculated. Staff costs have been approximately determined from knowledge of the average time per procedure and staff involvement. Patients have been followed up for one year.
Results: Twelve patients (28 per cent) with synthetic grafts required radiological intervention: 5 digital subtraction angiograms (DSA); 4 transfemoral arteriograms (TFA); 2 TFA with percutaneous transluminal angioplasty (PTA); 1 TFA with thrombolysis. Thirteen patients (34 per cent) with vein grafts required radiological intervention (5 DSAs; 7 patients had a total of 11 angioplasties; 2 patients had fistula embolisation, one with angioplasty). Five patients (8 PTAs) were dilated successfully. In 2 patients the graft re-occluded within days; successful lysis in one was followed by a patch plasty but the other failed and was left occluded without limb loss. Thrombolysis of the occluded synthetic graft was unsuccessful and limb salvage failed. DSA in 3 patients resulted in revision surgery (1 jump graft, 1 patch-plasty, 1 excision retained valve). The total cost for radiological intervention within the vein graft group was £5145 (median £395 per patient) and £1703 (median £142 per patient) for the synthetic group.
Conclusions: The surveillance programme resulted in a total of 25 angiograms, 13 PTAs, 3 thrombolyses and 2 embolisations. The workload generated is considerable, but worthwhile, and almost certainly cheaper than any surgical alternative. This study will lend weight to realistic funding for the radiological consequences of a graft surveillance programme.

Vascular 008

Outcome after intensive-care unit admission in vascular surgery patients

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Introduction: Little is known about the outcome of patients admitted to the intensive care unit (ICU) after vascular surgery. Outcome data will aid in planning for future ICU bed requirements,
Methods: A retrospective review of 82 patients admitted to the ICU following vascular surgery between January 1993 and May 1995 was undertaken. There were 58 male patients (71 per cent) and thirty-nine admissions occurred after elective surgery (48 per cent). The indications for surgery included abdominal aortic aneurysm surgery (50 patients, 61 per cent) and peripheral vascular reconstruction (20 patients, 24 per cent).

	Elective (n = 39)	Emergency (n = 43)
Consultant surgeon present	30 (77 per cent)	29 (67 per cent)
Consultant anaesthetist present	28 (72 per cent)	18 (42 per cent)
ICU mortality	5 (13 per cent)	10 (23 per cent)
In-hospital mortality	10 (26 per cent)	18 (42 per cent)

Conclusion: Despite a high level of consultant input to the mangement of critically ill patients with vascular disease, one third of emergency cases were performed in the absence of a consultant surgeon. The development of a full-time, dedicated vascular service during this period has addressed this fact. Identification of a 17 per cent in-hospital mortality among survivors from ICU provides further evidence to support the development of step-down/high-dependency facilities within all hospitals with intensive-care units.

Vascular 009

Randomised controlled trial of the effects of mannitol on renal reperfusion injury during aortic aneurysm repair

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Renal failure is a relatively common cause of mortality following aortic aneurysm surgery. Mannitol has a number of actions which may be protective in this situation. A randomised controlled trial was conducted to test the effects of mannitol on the renal injury associated with aortic aneurysm repair. Urinary albumin and N-acetyl glucosaminidase (NAG) levels were measured as sensitive indices of renal impairment.

Patients received either mannitol 0·3 g/kg (n = 15) or saline (n = 13) as a rapid intravenous infusion prior to aortic cross-clamping. One patient in the control group developed fatal postoperative renal failure but there was no renal failure in the mannitol group. Two patients in the mannitol group died from perioperative myocardial infarction. There were no statistically significant differences in postoperative blood urea, serum creatinine or creatinine clearance between mannitol and control groups. In the mannitol group there was a significant diuresis on the first postoperative day (2250 ml) compared to preoperatively (1557 ml; $P = 0{\cdot}007$). When compared to controls, mannitol-treated patients had lower mean (sem) postoperative levels of urinary albumin (160 + 32 vs 500 + 140 mg/mmol creatinine; $P = 0{\cdot}036$) and NAG (143 +34 vs 271 + 70 μmol/mmol creatinine; $P = 0{\cdot}04$) indicating a reduced level of sub-clinical glomerular and tubular damage.

In conclusion, this study demonstrates that mannitol has a protective effect against renal injury during infrarenal abdominal aortic aneurysm repair. It is a simple and inexpensive treatment without adverse effects. Further studies are required to evaluate the mechanism of action of mannitol, be it a haemodynamic effect, a free radical scavenging effect or a combination of the two.

Vascular 010

Laparoscopic aortobifemoral bypass in a canine model – video of technique and analysis of stress responses

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Purpose: To measure and compare the physiological, metabolic, and haemodynamic responses to aortofemoral bypass grafting by three techniques: 'open' or conventional laparotomy, laparoscopic-assisted or mini-laparotomy, and totally laparoscopic.
Methods: Twenty-four laboratory-bred hounds were randomised to one of three groups ('open', laparoscopic-assisted, or totally laparoscopic). Four sets of parameters were measured: *metabolic* (serial blood glucose, serum cortisol and insulin, plasma adrenaline, plasma noradrenaline, and dopamine levels), *inflammatory* or *haematological* (serial leucocyte and platelet levels), *haemodynamic* (intraoperative continuous cardiac output monitoring), and *catabolic* (24-hour urinary nitrogen excretion).
Results: Eight dogs underwent 'open' surgery, eight laparoscopic-assisted, and eight totally laparoscopic procedures. The technique of totally laparoscopic aortobifemoral bypass grafting is described. Intraoperatively, there were no significant differences in cardiac output (litres/minute) between the three groups when taken at three specific time-points. Serial platelet ($\times 10^9$/l) and leucocyte ($\times 10^9$/l) counts similarly showed no significant differences (ANOVA, $P < 0{\cdot}05$). Serial blood glucose (mg/dl) and cortisol (μg/dl) levels also reflected similar responses to surgery in all three groups ($P < 0{\cdot}05$), but insulin (μIU/ml) assays did not.
Conclusions: In a canine model, a totally laparoscopic approach to aortobifemoral bypass grafting *is* feasible. However, the haemodynamic, metabolic, and inflammatory responses to laparoscopic and laparoscopic-assisted aortofemoral bypass grafting are similar to those produced by conventional laparotomy graft placement.

Hepatobiliary/Pancreatic 1–10 *Wednesday 22 May, 14·45–16·30*

H&P 001

Day-case laparoscopic cholecystectomy

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Laparoscopic cholecystectomy (LC) is now the treatment of choice for patients needing cholecystectomy. The benefits over open operation are considerable and could potentially be extended if LC can be safely performed as a day case.

From a consecutive series of 537 patients undergoing LC, 68 patients underwent LC as a potential day-case procedure. There were 21 male and 47 female patients, the median age was 48 years and all were A.S.A. grade I. All patients underwent standard elective LC with operative cholangiography.

There was no mortality: 61 of the 68 patients were discharged on the day of operation; 7 patients stayed for one or more postoperative nights, 3 because of postoperative nausea, 2 because of a bile duct exploration and 2 because of a delayed start to their operation. One patient was readmitted on day 2 with abdominal pain which settled spontaneously and 1 patient was reviewed but not admitted on the 4th postoperative day because of an umbilical wound infection.

From the total series of 537 patients, 56 per cent potentially met our requirements for undergoing day-case LC, suggesting that there is a considerable patient group suitable for day-case LC.

In selected patients operated upon by experienced surgeons, LC can safely be performed as a day-case procedure, extending further the benefits of LC.

H&P 002

Comparative major complication rates after laparoscopic cholecystectomy – a district survey

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Eleven of the 16 surgeons in South Glamorgan undertake laparoscopic cholecystectomy. Between May 1990 and May 1995, 1580 procedures have been performed. These have resulted in 41 referrals for emergency ERCP within 30 days of surgery (2·6 per cent). No patients have been sent outside the region for ERCP and all post-cholecystectomy problems have passed through the ERCP unit, even if surgery for bile duct repair has been undertaken elsewhere.

ERCP was for unexplained abdominal pain (n = 19), jaundice (n = 14), persistent bile drainage (n = 7) and pancreatitis (n = 1). There were 8 major duct injuries (0·5 per cent) manifest as jaundice in 4 cases and a bile leak in 4 cases. There were 10 cases of bile leak from the cystic duct (0·6 per cent), 4 associated with unrecognised CBD stones. A total of 9 patients had retained CBD stones (0·6 per cent), 4 presenting with cystic duct leak, 3 with jaundice and 2 with abdominal pain.

Surgery was undertaken in three hospitals and the rate of laparoscopic cholecystectomy/surgeon/annum was 9, 19 and 54 respectively for the three hospitals. Bile duct injury rates were 2·3 per cent, 1·1 per cent and 0·3 per cent in the three hospitals whilst major complication rates (duct injury and bile leak) occurred in 4·6 per cent, 1·6 per cent and 0·8 per cent respectively. There was a significant correlation with the number of operations performed per surgeon per annum and both bile duct injury ($r^2 = 0{\cdot}83$) and major complications ($r^2 = 0{\cdot}65$).

These figures represent an accurate reflection of the problems of laparoscopic cholecystectomy within a single health district. Early ERCP plays a crucial role in both diagnosis and treatment of complications after laparoscopic cholecystectomy. It also appears that complications are more common in hospitals where fewer laparoscopic procedures are undertaken.

H&P 003

Laparoscopic cholecystectomy without operative cholangiogram: 2000 cases over a 5-year period in two district general hospitals

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The first 1000 cases from each of two District General Hospitals where operative cholangiograms are not performed during laparoscopic cholecystectomy have been analysed. Instead a selection policy was adopted where patients suspected of having common bile duct stones (history of jaundice, raised LFTs, pancreatitis, dilatation of CBD on ultrasound) are investigated preoperatively with ERCP and/or infusion IVC. 280 ERCPs and 106 infusion IVCs were performed. Common bile duct stones were found in 130 patients. Non-fatal complications of ERCP occurred in 20 patients (1 bile leak, 19 minor pancreatitis). Sixty-six (3·3 per cent) laparoscopic cholecystectomies were converted to open cholecystectomy. There were no major bile duct injuries. Minor duct injuries occurred in 6 patients (all treated with insertion of T Tube). Bilomas occurred in 7 patients (ultrasound drained). There were four postoperative deaths (2 CVAs, 1 cirrhotic liver failure, 1 inhaled vomit plus biliary leak). To date (median follow-up 30 months) only 14 patients have required postoperative ERCP for suspected retained stones in whom stones were found in 10.

Conclusions: With selective preoperative investigation laparoscopic cholecystectomy can be safely performed without operative cholangiography and a low incidence of symptomatic retained stones.

H&P 004

Laparoscopic cholecystectomy in the West of Scotland – the first 5 years

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Laparoscopic cholecystectomy has rapidly become the procedure of choice in the treatment of symptomatic cholelithiasis. Despite almost universal acceptance a comprehensive overview of the general introduction of this procedure remains unclear. The introduction of laparoscopic cholecystectomy to the West of Scotland has been prospectively audited between September 1990 and 1995. Individual patient datasheets were submitted by the operating surgeon with subsequent casenote and theatre record validation by a research nurse (96 per cent complete). A total of 48 surgeons in 19 hospitals have submitted prospective data on 7469 cholecystectomies, of which 5736 (77 per cent) were attempted laparoscopically (4930 completed). An overall conversion rate of 14·1 per cent remained relatively constant throughout, although the rate decreased with experience and showed wide variation between individual surgeons (4·6–37·7 per cent). The operating surgeon was a consultant in 69 per cent of cases. There were 18 deaths (0·3 per cent) after laparoscopic cholecystectomy, of which 8 involved surgical complications. There were 248 complications (4·3 per cent) including 43 bile leaks (0·75 per cent), 38 significant bleeds (0·67 per cent), 8 incisional herniae (0·14 per cent) and 3 bowel perforations (0·05 per cent). Further invasive intervention was required in 100 cases (1·7 per cent) with 76 patients (1·3 per cent) undergoing laparotomy. Bile duct injuries occurred in 35 patients (0·61 per cent) with the annual incidence falling to 0·27 per cent from an apparent plateau of 0·75 per cent. Operative cholangiography was performed in 502 patients (8·8 per cent). In conclusion laparoscopic cholecystectomy has been successfully introduced with a low associated morbidity. The late downward trend in iatrogenic injuries suggests a prolonged 'learning curve'.

H&P 005

The impact of laparoscopic cholecystectomy: a nationwide audit

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The number of cholecystectomies (laparoscopic LC and open OC), and bile duct explorations (ECBD), age, sex ratio, proportion of emergency procedures, postoperative hospital stay, 30-day mortality, and use of endoscopic retrograde cholangiography (ERCP) before and after cholecystectomy were calculated on an annual basis from 1981 to 1994 using a mainframe computer analysis of hospital discharge and death certificate data for the whole of Scotland.

Over the 1980s, there was a modest but steady decline in the number of cholecystectomies performed (4495 in 1981 to 4043 in 1990 – a fall of 10 per cent). The introduction of LC was associated with a 20 per cent increase in the number of cholecystectomies (4861 in 1994). In 1994, LC accounted for 65 per cent of procedures. Over the period 1981–94, there was a gradual fall in mortality: in 1981–84 there were 60 (0·4 per cent) deaths, in 1985–89 41 (0·2 per cent) deaths and 1990–94 18 (0·1 per cent) deaths (χ^2 26, 2 d.f., P < 0·0001). From 1990–94, 9455 LCs were performed with only three deaths (0·03 per cent). LC patients were younger and a higher proportion female but a smaller proportion were emergency admissions (9 per cent vs 22 per cent for OC). The introduction of LC was associated with an increased use of ERCP before and after surgery (10 per cent and 4 per cent of cases respectively in 1994) and a fall in the proportion of all patients undergoing ECBD (13 per cent in 1989 to 6 per cent in 1994). There was gradual reduction in hospital stay after OC from a median of 8 days (interquartile range 7–11) in 1981 to 5 (4–7) in 1994. Median hospital stay for LC was 2 (1–3) days.

In conclusion, LC has resulted in a lower threshold for surgery and in a dramatic reduction in postoperative hospital stay. Operative mortality has fallen by two-thirds over the past 14 years which may in part be attributable to the benefits of LC.

H&P 006

Pancreatic debridement for fulminant acute pancreatitis

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The timing and nature of intervention in patients with complicated acute pancreatitis is controversial. At present we carry out pancreatic debridement (PD) in the presence of infected sequestra/collections or with worsening of the clinical condition of the patient despite maximal conservative support. We have reviewed our experience of PD in these very ill patients.

From a series of 144 patients presenting to one consultant over 7 years, 27 patients underwent PD (18 men, 9 women, mean age 57 (range 28–84) years. The aetiology was gallstones in 5 patients, alcohol in 6, post ERCP in 3 and unknown in 13. 20 were tertiary referrals from other surgeons. All patients had contrast CT scans. The mean APACHE II score on admission to our unit was 10·2 (range 2–25).

A mean of 27 days after presentation each patient underwent PD. 19 patients died and 8 survived. The mean stay was 51 days (range 2–118). The APACHE II score at operation was the only independent predictor of survival (P < 0·02, 8·65 vs 14·2). The tertiary referrals fared significantly worse than patients presenting locally (P < 0·03).

Given the overall poor outcome, the fact that the APACHE II score provided such a good predictor of outcome (APACHE II < 10, 6 of 10 survived, APACHE II > 10, 2 of 17 survived P < 0·001) and the finding that patients admitted to us early in their attack fared better, we are now questioning our policy of delayed intervention. Patients with severe acute pancreatitis should be treated in a specialist unit and early consideration given to operative intervention in the face of a poor response to conservative measures.

H&P 007

Outcome of acute pancreatitis in the over-seventies

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Over the 5-year period, May 1990 to May 1995, 60 patients with acute pancreatitis over the age of 70 years were admitted to a unit with a special interest in pancreatico-biliary disease. There were 22 men and 38 women with ages ranging from 70 to 99 years. The majority had gallstone-related disease ($n = 38$) and alcohol was implicated only in one patient. Thirty-seven admissions were for mild pancreatitis (Imrie's score </=2) and 26 for severe pancreatitis (Imrie's score >/=3). Three patients with severe disease were admitted to an intensive care unit and four of them died. The overall mortality was 24 per cent ($n = 14$), representing 4 deaths (11 per cent) in the mild group and 10 (39 per cent) in the severe group. Intervention was required in 30 patients – ERCP in 23 and surgery in 11. Three patients died following surgery, two after pancreatic necrosectomy and one following drainage of a peri-pancreatic collection. The mortality from acute pancreatitis in the elderly patient in our practice is higher than in the general population (24 per cent vs 6 per cent) and a greater proportion of the elderly had a severe form of the disease (43 per cent vs 25 per cent). The mortality following surgery however was lower than in younger patients in an earlier study from this centre (27 per cent vs 34 per cent) and the decision to operate should not be withheld on the grounds of age alone. Of the 23 elderly patients with predicted severe disease, 13 returned to their previously existing quality of life.

H&P 008

A surgical approach to chronic pancreatic pseudocysts

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The advent of non-operative drainage techniques has led to re-evaluation of the traditional surgical approach to pseudocysts in chronic pancreatitis. A personal series of 95 patients operated between 1978 and 1995 included 73 men (77 per cent) and 22 women with a mean age of 43 years (range 15–75 years). All patients had established chronic pancreatitis caused by alcoholism ($n = 67$, 71 per cent), recurrent acute pancreatitis ($n = 14$) or unknown agents (14). Cysts either arose insidiously ($n = 59$) or followed an acute exacerbation of pancreatitis (post-necrotic, $n = 36$). Multiple in 24 patients (25 per cent), cysts were distributed equally within the gland: head 40, neck 26, body 41, tail 29. Mean cyst diameter was 7·2 cm, and they were classified as small (<5 cm) in 28 patients, medium (5–10 cm) in 45 and large (>10 cm) in 22. Complications in 38 per cent of patients included jaundice ($n = 12$), infection (8), haemorrhage (6), gastric outlet obstruction (3), pancreatic ascites (2) and persistent fistula following percutaneous drainage (5). Cyst drainage was undertaken in 39 patients (41 per cent) with concomitant drainage of the pancreatic duct in 16. Resection in 56 patients (59 per cent) entailed distal ($n = 33$), proximal (16) or total pancreatectomy (7). The only death followed subsequent erosion of the portal vein into the cyst cavity. Resection was generally preferred to drainage for small cysts (29 vs 9: P = 0·06) and for cysts in the body and tail (32 vs 19: P = 0·5).

H&P 009

Comparison of metal and plastic stents for the relief of malignant biliary obstruction

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In the management of malignant obstructive jaundice, metal stents are said to remain patent for a longer period of time than plastic ones due to their calibre and may be associated with less post-procedural complications due to the use of narrower introducing sheaths. Over a 2-year period, 66 patients underwent percutaneous placement of biliary endoprosthesis as the primary and sole definitive treatment of their malignant biliary obstruction following failure of endoscopic stenting. Thirty-two patients had metal stents and the remaining 34 had plastic stents inserted. Patients in both groups were matched for age, sex, site of biliary obstruction and degree of jaundice. There was no significant difference between the median survival of the metal group (74 days) and the plastic group (98·5 days). The plastic stents remained patent for an average of 97·7 days (range 15–201 days) whereas the metal stents were patent only for an average of 72·3 days (range 29–142 days). Sixty per cent of patients who had a metal stent needed a second procedure for blocked stent before death while 47 per cent of those with plastic stents required a second procedure. Two patients in each group died within a week of and as a consequence of the procedure, while an additional 4 patients with plastic stents died within 30 days. In this non-randomised study, metal stents had no obvious advantage over plastic stents in the relief of malignant biliary obstruction.

H&P 010

Pancreatoduodenectomy for tumours: an experience of 200 procedures

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Excision is the time-honoured procedure for treatment of tumours in the head of the pancreas, yet the mortality and morbidity of such procedures remain high and the outcome poor. A personal series is reviewed to determine whether a selective policy improves results.

Patients presenting with tumours in the pancreatic head were carefully assessed and imaged by endoscopy, ultrasound and CT scanning to determine operability. Only patients who were deemed fit and who were thought to have operable tumours (≤ 3 cm in size, no local invasion or distant disease) were selected,

Tumours resected were ampullary in 71, pancreatic ductal in 63, bile duct in 19, neuro-endocrine in 17 and miscellaneous in 30 (10 malignant, 20 benign). The 60-day mortality was 6·0 per cent. The median survival in months following resection for ampullary tumours was 20, pancreatic ductal 13, bile duct 16 and malignant miscellaneous 37. Five-year survival was 35 per cent for ampullary tumours and 15 per cent for pancreatic ductal tumours. Survival was related to tumour size, lymph node status and resection margin involvement.

Despite improved operative survival, the outlook remains gloomy. Nevertheless, the important improved survival in the miscellaneous group emphasises the need to define the exacy pathology and treat accordingly.

Breast 001

Cyst type and breast cancer risk

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Two types of cyst have been identified. Apocrine cysts, or type I cysts, have a ratio of $[\mathrm{Na}^+]/[\mathrm{K}^+] < 3$ and flattened cysts, or type II cysts a $[\mathrm{Na}^+]/[\mathrm{K}^+] \geq 3$. 3041 cyst fluids were aspirated from 1374 patients and $[\mathrm{Na}^+]$ and $[\mathrm{K}^+]$ measured from 1981 to 1989. From Cancer Registry data 60 patients had developed breast cancer by the end of 1993. Patients were classified into three groups, those who had type I cysts only at presentation (n = 451), those with type II cysts only (n = 741) or mixtures of the two types (n = 182).

A Cox proportional hazards regression analysis has been performed relating breast cancer risk to (i) cyst type at presentation, (ii) the age of the patient at presentation and (iii) the number of cysts aspirated at the first clinic visit. No significant difference in cancer incidence was evident between patients classified on the basis of cyst type, in particular the 95 per cent confidence interval for ratio of patients with type II to type I cysts who subsequently developed breast cancer was 0·47–1·39. Similarly, neither age nor numbers of cysts aspirated at the initial clinic visit was significantly associated with subsequent cancer incidence. If there is an increased risk of breast cancer in patients with type I cysts, then the magnitude of this risk is less than two.

Breast 002

Axillary node sampling in breast cancer – an assessment of its efficacy

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Some surgeons have been unable to dissect out 4 separate nodes from the axilla. Reports have also indicated that as increasing numbers of nodes in the lower axilla are sampled, so the chance of identifying involved nodes increases. The accuracy of 4-node axillary sampling has thus been questioned.

Three hundred and ninety-two patients undergoing consecutive axillary node sampling performed by all grades of surgeons have been studied. The number of nodes removed ranged from 0 to 12 and only 19 patients had fewer than 3 nodes in the specimen submitted for pathology (Table). The mean number of nodes sampled was 4·8 with a standard error (SE) of 0·16 and the median was 4. The percentage of patients who were node-positive did not increase significantly as the number of nodes increased (Table). Mean number of nodes sampled when axillary node-negative was 4·6 (SE 0·10) and 4·89 (SE 0·24) when nodes were involved.

Number of nodes found	0	1	2	3	4	5	6	7	8	9	>9
Number of pts	2	9	8	50	148	101	33	10	8	8	15
Percentage with involved nodes	0	33	38	28	21	22	18	30	13	38	47

These data show that it is possible to dissect out 4 axillary nodes consistently and the chances of identifying involved nodes does not increase significantly as the number of nodes sampled increases. This technique should be more widely used, particularly for patients with a low probability of nodal involvement.

Breast 003

Locoregional recurrence and survival in patients with involved cavity biopsy following wide excision for early breast cancer

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Following wide excision for early breast cancer, approximately 20 per cent of patients have microscopic DCIS or invasive carcinoma in biopsies taken from the excision cavity. In the majority of cases this represents multifocality rather than residual disease. We have investigated whether a positive bed biopsy influences locoregional recurrence and overall survival.

A consecutive group of 268 patients with early breast cancer was treated by wide excision, axillary clearance and breast radiotherapy. All patients underwent a four quadrant bed biopsy and have been followed for a minimum period of five years.

In 68 patients (25 per cent) the bed biopsy was reported as positive (63 invasive and 4 DCIS). Twenty-two underwent mastectomy because of disease in more than two bed biopsies and an aggressive degree of differentiation.

Multivariate analysis for locoregional recurrence showed a relationship with lymph node status, size of tumour and bed biopsy positivity. There was no statistically significant difference however in overall survival between bed biopsy positive and bed biopsy negative patients (RR 1·21 [95 per cent CI = 0·63–2·31] P = 0·56).

This study demonstrates that a positive bed biopsy following wide local excision does not influence overall survival although the incidence of locoregional recurrence is increased. In patients in whom local recurrence does occur mastectomy is the treatment of choice.

Breast 004

Tumour bed positivity predicts outcome after breast-conserving surgery

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Local recurrence after breast-conserving surgery is caused by residual disease and is strongly associated with a short distant disease-free survival.

The aim of this study was to determine the incidence of tumour bed positivity (residual disease) after breast-conserving surgery and correlate it with disease outcome and established prognostic factors.

In 300 patients undergoing breast-conserving surgery, tumour bed positivity was detected by taking a shaving from the surgical excision cavity. Re-excision was performed on 41 patients (13·7 per cent) where extensive disease was found. Axillary lymph node status, oestrogen receptor (ER) content, tumour size and grade were recorded. Tumours were immunohistochemically stained for CerbB2 and p53. Mean follow up was 4·5 years.

The local recurrence rate was 2 per cent (6/300) and systemic recurrence rate 12 per cent (36/300). The incidence of tumour bed positivity was 39·3 per cent (118/300) and correlated with short disease-free (χ^2 test, $P < 0{\cdot}01$), distant disease-free (χ^2 test, $P < 0{\cdot}05$) and overall survival (χ^2 test, $P < 0{\cdot}05$). Combining tumour bed positivity with established prognostic factors identifies subgroups of patients with a particularly poor prognosis (systematic recurrence rate ranging from 24·1 per cent to 46·7 per cent).

In addition to determining risk of local recurrence, tumour bed positivity provides important prognostic information after breast-conserving surgery.

Breast 005

Use of magnetic resonance screening for imaging bone metastases

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Magnetic resonance imaging (MRI) is the most sensitive radiological method of detecting bone metastases. In breast cancer, MRI has been reported to detect early tumour infiltration of the marrow of clinical significance. We have reviewed the use of MRI in imaging of bone and assessed its role as a pre-operative staging procedure in breast cancer.

Thirty-two patients underwent both MRI and radioisotope bone scan (23 breast cancer, 9 others). In 9 (28 per cent) cases MRI demonstrated bone metastases which had not been evident on bone scan and in 4 cases suspicious lesions on bone scan proved to be due to degenerative changes or fracture on MRI. Asymptomatic spinal cord compression was diagnosed in 3 cases. A total of 16 (50 per cent) MRI scans provided additional information which influenced management.

Pre-operative MRI scans in 20 asymptomatic women, mean age 55 (range 39–81), taken prior to their primary surgery for breast cancer, have identified abnormalities in 4 (20 per cent) cases, with multiple deposits in 2. Radioisotope scanning was normal in 3/4 cases.

MRI provides additional information to that found by radioisotope scans in symptomatic patients. In pre-operative patients, it may be useful in highlighting a subgroup of patients which would benefit from systemic therapy.

Breast 006

YNZ22 allele loss, not p53 mutation, is associated with breast cancer prognosis at 5 years

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Two common genetic abnormalities on the short arm of chromosome 17, YNZ22 allele loss (from 17p13.3) and p53 mutation (at 17p13.1), may be associated with prognosis in breast cancer. The aim of this study was to prospectively compare these two genetic events to disease behaviour.

Deoxyribonucleic acid (DNA) was extracted from blood/tumour pairs of 91 patients with primary operable breast cancer. Southern blots of DNA probed with YNZ22 demonstrated allele loss in 33/63 (52 per cent) informative patients of whom 24/63 (38 per cent) had advanced disease or had died at 5 years. YNZ22 allele loss was associated with poor prognosis (chi square 4·2, $P = 0{\cdot}04$, df1). p53 mutation, detected in the cancer of 10 (16 per cent) of these 63 informative patients using the amplification mismatch technique, was not associated with disease behaviour.

This study has identified YNZ22 allele loss rather than p53 mutation as a marker of poor prognosis in breast cancer at 5 years and suggests that studies to identify a further breast cancer gene on 17p13.3, distinct from p53, are required.

Breast 007

The quantitative importance of oestrogen receptor (ER) assays in elderly patients with breast cancer treated with tamoxifen

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Not all breast cancers respond to tamoxifen; we have therefore examined two types of oestrogen receptor assay in relation to response. In 48 elderly (64–87 years) patients with primary breast cancer (T2–T4, N0–2 M0), receptor assays were performed on two samples of tumour: (1) a fine needle aspirate (by immunocytochemical assay, ER-ICA) and (2) a subsequent wedge biopsy (by enzyme-immunoassay, ER-EIA). Patients with histologically proven cancer and ER-moderate/rich tumours (≥20 fmol/mg protein by ER-EIA, specimen to contain ≥ 10 per cent tumour cells) were then treated with tamoxifen (20 mg/day) for 3 months prior to definitive surgery; during that period, tumour size was monitored at monthly intervals by ultrasonography.

Thirty-eight out of forty-eight (79 per cent) patients showed significant shrinkage (≥ 10 per cent) over the 3-month period; the average reduction in size for these 'responders' prior to definitive surgery was 60·3 per cent. When 'response' (per cent shrinkage at 3 months) was examined in relation to several parameters (T stage, N stage, age, initial tumour volume, histological grade, tumour cellularity, soluble protein content, ER-ICA and ER-EIA results), only the result of the biochemical assay (ER-EIA) was of significant predictive value ($P = 0{\cdot}0001$) by multivariate analysis. 'Response' was significantly correlated with the concentration of ER (fmol/mg protein) in the tumour ($r = 0{\cdot}71$, Spearman's Rank test).

This study underscores the importance of *quantitative* measurements of oestrogen receptor concentration in deciding which patients are likely to benefit from tamoxifen treatment.

Breast 008

Changes in TGFβ mRNA expression in breast cancer patients treated with tamoxifen

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Treatment with tamoxifen is an important therapeutic modality in patients with breast cancer. The exact mechanism of tamoxifen's action has not been defined and some have suggested that the growth suppressive effects of transforming growth factor betas (TGFβs) are involved. This study has examined changes in the expression of the mammalian isoforms of TGFβ mRNA in a series of breast cancer patients treated with tamoxifen. Forty-one patients treated with tamoxifen for between 2 and 10 months had clinical response determined by serial ultrasound measurements of the tumours. Tissue was obtained from each primary tumour before and during the course of treatment and assessed for TGFβ isoform expression by RNAase protection assay. Semi-quantitative measurement was determined by scanning densitometry. Of the 41 patients treated, 27 of 41 patients showed a clinical response (minimum decrease in tumour size of 10 per cent over the treatment period) and 14 showed no response. No relationships were apparent between clinical response and changes in levels of either $\text{TGF}\beta_1$ or β_3, however, there was a significant trend for responding patients to show increasing $\text{TGF}\beta_2$; 14 of 27 responders showing an increase compared to 2 of 14 non-responding patients ($P = 0{\cdot}037$). The present study has failed to show generalised changes in expression of TGFβ mRNA with clinical response to tamoxifen.

Breast 009

Apolipoprotein D, a new antioestrogen marker in the breast

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Tamoxifen, an antioestrogen, is being assessed as a long-term chemopreventative agent in patients at high risk of developing breast cancer.

Surrogate markers of tamoxifen action on the normal breast are needed to assess its action in individual women. Two proteins, one induced (pS2) and one inhibited (Apoliprotein D) by oestrogen stimulation of breast cell lines, were measured in nipple secretions from normal women, and women with breast pain treated with LHRH agonists or tamoxifen, to determine if they could be used as antioestrogen markers. ApoD and pS2 were measured by radioimmunoassay and total protein by the Bradford method.

	Normal	Breast pain	Pain after 3/12 Zol.	Pain after 3/12 Tam.
n	63	15	9	6
Median pS2	9·81	27·8	6·53	4·25
Range ng/mg protein	0·26–260·5	0·5–166·8	0·12–38·7	0–25·03
Median ApoD	194	59·9	525·0	266·0
Range µg/mg protein	12–1833·1	8·9–212·7	34–861	188·5–1772·7

Premenopausal secretion levels of pS2 were higher ($P < 0{\cdot}02$) and ApoD lower ($P < 0{\cdot}03$) than postmenopausal levels. After Zoladex and tamoxifen treatment, secretion pS2 levels fell (both $P < 0{\cdot}02$) and ApoD levels rose significantly ($P < 0{\cdot}03$ and $P < 0{\cdot}02$ respectively). pS2 and ApoD may prove useful intermediate markers of tamoxifen action. LHRH-leutenising hormone releasing hormone. Stats: Mann–Whitney and Kruskal–Wallis tests.

Breast 010

Are activators of coagulation or fibrinolysis better prognostic indicators in breast cancer?

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Besides the procoagulant tissue factor (TF), the fibrinolytic agent urokinase (uPA) facilitates tumour invasion and its receptor (uPAR) is an independent predictor of outcome in colorectal cancer. We have studied 136 women with invasive breast cancer to determine the relative prognostic value of activators of coagulation or fibrinolysis. At operation, 100 women were node-negative, 27 had 1–3 nodes and 9 > 4 nodes. Sixty-six per cent were post-menopausal and 70 per cent oestrogen-receptor (ER) positive. Histological differentiation was as follows: 27 grade I, 44 grade II and 65 grade III. Tumour lysates were assayed for TF, uPA or uPAR using ELISA techniques. There were 7 deaths during a median follow-up of 50 months (range 2–144) and 28 patients had recurrent disease at a median time of 12·5 months (IQR 4–54). The median tumour TF content was 63·5 pg/mg, uPA 0·15 ng/mg and uPAR 0·42 ng/mg. Univariate analysis revealed high TF content ($P = 0{\cdot}03$), advancing age ($P = 0{\cdot}04$) and post menopausal status ($P = 0{\cdot}04$) to be associated with early recurrence and node status ($P = 0{\cdot}007$), histological grade ($P = 0{\cdot}04$) and tumour size ($P = 0{\cdot}002$) with early death. A Cox multivariate analysis for disease free survival was as follows:

	Hazard ratio	*P* value
Menopause	0·46	0·05
TF	1·1	0·02
uPA	1·56	0·23
uPAR	1·17	0·63

The procoagulant TF is the more powerful predictor of poor outcome in this disease.

UGI 001

Anti-reflux surgery: its role in bile reflux

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Proton pump inhibitors and fundoplication both control acid reflux, but their specific roles in the treatment of GORD remain uncertain. The introduction of a fibre-optic probe has made ambulatory bile measurements possible. This study examines bile and acid reflux before and after anti-reflux surgery in a group of patients with non-Barrett's reflux.

Methods: 20 patients were entered into a prospective study. All had preoperative manometry, bile and pH studies. From the pH studies a DeMeester Acid Score was calculated. Bile studies were analysed to determine the frequency of associated bile reflux in GORD. To date 7 patients have been studied postoperatively.

Results:

	Preop	Postop
LOSP (mm Hg)	7·1 (3–12)	15 (15–18)*
Acid score mean (SEM)	55·4 (9·2)	2·9 (0·3)*
Bile reflux (Per cent absorbance >0·14)	42 (0·6–81)	1·1 (0–3·3)*

Mann–Whitney U-test *$P < 0{\cdot}05$. LOSP = lower oesophageal sphincter pressure.

Preoperative LOSP was significantly increased after surgery. Four patients with bile reflux preoperatively had significantly decreased bile levels postoperatively.

Conclusion: Patients with acid reflux frequently have bile reflux also. Anti-reflux surgery protects against both acid and bile reflux and thus confers an advantage over life-long proton pump blockage with the potential risks attendant on achlorhydria.

UGI 002

Simple laparoscopic gastropexy for rolling hiatal hernia

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Rolling hiatal hernia comprises 2–5 per cent of all hiatal hernias. It presents a major challenge in management since many of the patients are unfit for formal surgical repair. We have used a simple laparoscopic modification of the Boerema gastropexy in 7 patients. All had severe symptoms and most were unfit for conventional surgery. Four or five laparoscopic cannulas were inserted. The stomach was reduced into the abdomen and fixed to the anterior abdominal wall with two Goretex sutures tied extracorporeally,

There was one postoperative death due to spontaneous intrathoracic perforation of the posterior aspect of the stomach in an elderly woman with severe cardiac disease. This was not recognised at the time of operation. The remaining patients have no obstructive or reflux symptoms and there have been no recurrences to date.

Simple laparoscopic gastropexy may well be the treatment of choice for rolling hiatal hernia.

UGI 003

Intraoperative laparoscopic ultrasonography in the staging of gastro-oesophageal malignancy

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Thirty per cent of gastro-oesophageal carcinomas which appear operable following conventional staging are irresectable at the time of surgery. Laparoscopy combined with high-frequency, high-resolution ultrasonography scan may optimise the assessment of resectability of such tumours.

In addition to conventional staging (full blood count, liver function tests, chest X-ray, abdominal ultrasonography, computed tomography (CT) and upper gastrointestinal endoscopy), 47 patients with gastric or oesophageal tumours had laparoscopic intraoperative ultrasonography (5 mHz Aloka probe) to visualise the primary lesion (where possible) and evaluate loco-regional or hepatic spread.

Of the 40 patients not excluded by conventional staging techniques, 2 await completion of neo-adjuvant chemotherapy and 1 was unfit for major surgery. Seven (18 per cent) patients deemed resectable by conventional staging techniques were excluded from surgical intervention following laparoscopic ultrasound (peritoneal metastases, involvement of vital structures or liver metastases).

Of the 30 attempted resections only 1 (3 per cent) proved inoperable due to extensive intra-thoracic malignancy. The remaining 29 patients (97 per cent) were correctly predicted to have resectable lesions. Of these only 1 (3 per cent) was palliative, 3 (9 per cent) had histological evidence of residual disease and 26 (87 per cent) were potentially curative.

UGI 004

The relationship between bile acid reflux and oesophageal pH

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Reflux of duodenal contents in the oesophagus, presumed to be the cause of 'alkaline' exposure, may play a critical role in the development of complications of gastro-oesophageal reflux disease (GORD).

The aim of this study was to investigate the temporal association between oesophageal pH and bile acid reflux in patients with reflux oesophagitis using a new automated oesophageal sampling device.

Oesophageal sampling studies with simulateneous pH monitoring were performed on 40 subjects (10 normal and 30 patients with GORD) over 15 hours using a double lumen nasal tube incorporating an antimony pH electrode. The samples were analysed for 14 fractions of bile acids using high-performance liquid chromatography.

The highest levels of bile acids were detected in samples from patients with oesophageal stricture and Barrett's with predominance of taurine conjugates ($P < 0{\cdot}05$ vs normal, minimal and erosive oesophagitis; Wilcoxon). These patients also had maximum acid exposure (pH < 4). There was no difference in the alkaline exposure (pH > 7). Although there was no differential correlation between total bile acid concentrations and intraoesophageal acid or alkaline exposure, the taurine conjugates were seen to correlate with acid exposure ($r = 0{\cdot}27$, $P = 0{\cdot}05$; Spearman's) while glycine conjugates were detected mainly in the alkaline pH range ($r = 0{\cdot}32$, $P = 0{\cdot}04$).

The study supports the theory that duodenogastric reflux and the stomach acidity interrelate by altering the pH and enzymatic activity of the refluxed juice to modulate the injurious effects on the oesophageal mucosa.

UGI 005

Complications of oesophagectomy: an audit of 700 cases

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The outcome following resection for oesophageal cancer is poor, but surgery offers the best palliation in locally advanced disease and the best hope of cure for early lesions. This study examined the complications of surgery from a database of 700 cases in the 24-year period to November 1994.

Method: The database was analysed for specific complications in the following categories: respiratory, cardiac and renal complications, anastomotic leak, haemorrhage, chylothorax, recurrent nerve palsy and need for reoperation.

Results: Of 700 patients, 73 had pharyngolaryngo-oesophagectomy, 11 had intubation and 16 had insufficient data, leaving 600 for analysis. Operations performed were 249 Lewis-Tanner, 173 3-stage, 144 abdominal/left chest, 22 transhiatal and 12 other.

	Complication rate	Complication mortality
Respiratory	336 (56 per cent)	27 (5 per cent)
Cardiovascular	168 (28 per cent)	18 (3 per cent)
Anastomotic leak	42 (7 per cent)	26 (4 per cent)
Chylothorax	8 (1 per cent)	5 (1 per cent)
Haemorrhage	27 (5 per cent)	13 (2 per cent)
Recurrent nerve palsy	17 (3 per cent)	3 (1 per cent)

Conclusions: Respiratory complications were the most frequent, but the most devastating were chylothorax and anastomotic leak. Vigilant postoperative surveillance and early intervention are the essentials of management of postoperative complications.

UGI 006

Patients achieve a good quality of life after potentially curative surgery for oesophageal cancer

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Surgical resection is the mainstay of potentially curative treatment for patients with oesophageal cancer. However, this entails major radical surgery. Whilst excision of the tumour may improve patients' quality of life in terms of their ability to swallow, it has been suggested that their overall quality of life may be diminished.

We assessed the physical performance (WHO score 0–4), physical and social ability (Troidl index 0–14) and psychological state (hospital anxiety and depression score 0–42) in 30 patients (M:F 18:12, median age 68) who underwent potentially curative resection for oesophageal cancer. Twenty-five patients underwent Ivor Lewis oesophagectomy and 5 patients a total three-stage total oesophagectomy. We compared their results with those of 32 age-matched controls who had not undergone surgery.

Results:

	Controls (per cent)	Patients (per cent) Preop	1 month	3 months	6 months
WHO (0–1)	100	96	13	80	96
Troidl (>7)	97	77	27	53	80
HAD (16)	94	96	93	96	96

As expected, the quality of life of these patients was poor initially after such major surgical intervention. However, by six months the majority of these patients had achieved a satisfactory quality of life.

UGI 007

Delay in treatment for oesophageal cancer

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Dysphagia is the most frequent presenting symptom of oesophageal cancer, but many patients present late. This prospective study analysed duration of symptoms and reasons for delay in patients presenting with oesophageal cancer.

Method: One hundred patients were interviewed using a standard questionnaire. Delay in presentation was from onset of dysphagia to first presentation to GP. Time interval to treatment was from the onset of dysphagia to definitive treatment.

Results: Seventy-nine patients presented with dysphagia over a 24-month period. Seventy per cent of patients waited 12 weeks or more for treatment and 20 per cent waited more than 26 weeks. The most common cause for delay was lack of awareness of significance of symptoms but the longest delays were due to hospital services.

	Delay to GP (weeks)		Interval to treatment (weeks)	
	Mean	Range	Mean	Range
Patients with dysphagia	8	(1–34)	17	(1–52)
Other symptoms	5	(1–13)	17	(1–30)
All patients	7	(1–52)	17	(1–52)
Male	8	(1–52)	18	(1–52)
Female	6	(1–34)	14	(1–52)

The difference in delay between males and females was not significant ($P = 0{\cdot}158$).

Conclusion: The mean interval to definitive treatment was 17 weeks. Delays were as follows: one-third at patient level, one-third at GP level and one-third at hospital level. Increased awareness of the significance of dysphagia would permit earlier diagnosis and treatment.

UGI 008

Laparoscopic surgery for paraoesophageal hiatus hernia

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Paraoesophageal hernia is a rare but potentially fatal condition, occurring predominantly in the elderly. Open surgery has been shown to be safe and effective. This condition may now be treated by laparoscopic surgery.

Twenty-five patients (3M:22F), 77 (53–89) years, have undergone laparoscopic surgery in four centres. Symptoms (vomiting/chest pain) were present for 48 (1–144) months. Diagnosis was by barium radiography in all. Median ASA grade was 2 (1–3) and anaesthetic time was 92 (58–182) minutes. Three patients required conversion due to inability to reduce the stomach, kyphoscoliosis and adhesions. Three different methods of repair were used: mesh repair with gastropexy (n = 6); mesh repair with gastrotomy (n = 7); sutured left diaphragmatic gastropexy without crural repair (n = 12). Postpoperative inpatient nights were 3 (1–6); 7 (6–20) and 2 (2–5) respectively. One died 4 days postoperatively (conversion). Two had chest complications and 1 prolonged gastric drainage. Four patients require medical treatment for heartburn and 1 has required reoperation for further gastric herniation 3 months postoperatively. Of 23 patients alive 24 (3–30) months postoperatively all are Visick 1 & 11.

Laparoscopic surgery is both feasible and safe for patients with rolling hiatus hernia.

UGI 009

A learning curve for laparoscopic fundoplication is definable and at least partly avoidable

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To determine whether a learning curve for laparoscopic fundoplication can be defined and steps taken to avoid it, the outcome of 320 procedures undertaken by 11 surgeons over 46 months was analysed in 3 ways: (1) the group experience; (2) each individual surgeon's series; (3) early vs late beginners.

Complication, conversion and reoperation rates were all higher in the first 50 procedures performed by the whole group and the first 20 procedures performed by each surgeon. Adverse outcomes were less likely when surgeons commenced fundoplication later in the series when experienced supervision was available. Disregarding each surgeon's first 20 procedures, created a subset of 174 patients operated on by 5 'experienced' surgeons. Median operation time was 80 minutes with 91 per cent of patients satisfied with their outcome up to 2 years after surgery; 10·3 per cent still reported some solid food dysphagia at 12 months. Complications occurred in 5 per cent, with 2·3 per cent requiring early reoperation and 3·4 per cent late reoperation.

The early overall outcome of laparoscopic fundoplication in experienced hands is comparable with open surgery. A learning curve can be defined and adverse outcomes minimised during an individual's learning curve by providing experienced supervision during the first 20 cases.

Vascular 011

Is patch angioplasty required for large arteries after carotid endarterectomy?

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Routine patch angioplasty has been advocated following carotid endarterectomy since the reported incidence of restenosis is reduced. This study assesses the effect of selective patching of smaller arteries on the rate of restenosis.

A consecutive series of 212 patients underwent carotid endarterectomy performed by one surgeon. Following endarterectomy a 5-mm Dacron patch was selectively employed for caliper-measured distal internal carotid arteries of less than 5 mm (group 1, 95 patients) or less than 6 mm (group 2, 118 patients). Forty-five patients (47 per cent) in group 1 and 72 patients (61 per cent) in group 2 received patch angioplasty. Patients were followed prospectively for a mean of 32 (group 1) and 12 (group 2) months with duplex scanning at 1 day, 1 week, 3, 6, 9 and 12 months, and yearly.

Life table analysis with log rank test revealed:

	Patch	Non-patch	Significance
Restenosis >50 per cent:			
Group 1 (24 months)	14 per cent	24 per cent	$P = 0\cdot4$
Group 2 (12 months)	13 per cent	11 per cent	$P > 0\cdot5$
Survival:			
Group 1 (24 months)	96 per cent	86 per cent	$P = 0\cdot4$
Group 2 (12 months)	100 per cent	93 per cent	$P > 0\cdot5$
Stroke:			
Group 1 (24 months)	6 per cent	9 per cent	$P > 0\cdot5$
Group 2 (12 months)	0	4 per cent	$P = 0\cdot4$

This study shows that if patch angioplasty is used selectively for distal internal carotid diameters of less than 6 mm, equivalent outcomes are achieved for patched and non-patched patients, while minimising the requirement for patching.

Vascular 012

Carotid endarterectomy and contralateral carotid occlusion: is it 'high-risk' surgery?

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Seven hundred patients undergoing carotid surgery in the UK and Ireland during a six-month period from 1/3/1994 to 31/8/1994 were prospectively studied. One hundred and eight cases had a contralateral internal carotid occlusion. Previous studies have suggested a stroke risk of around 10 per cent for such cases.

Indications for surgery in the present series were: transient ischaemic attack 29 (26·9 per cent), amaurosis fugax 22 (20·4 per cent), cerebrovascular accident (CVA) 31 (28·7 per cent) and 'others' 26 (24 per cent). Ischaemic heart disease was present in 47·2 per cent, hypertension in 53·7 per cent and diabetes in 22·2 per cent. Preoperative arteriograms were performed in 57·4 per cent. Mean ipsilateral stenosis was 82 per cent (range 30–99 per cent). Thirty-one per cent of patients had preoperative neurological consults. Shunts were used in 83·3 per cent (vs 64·7 per cent with no occlusions; $\chi^2 = 1\cdot29$; P = n.s.); tacking sutures were used in 48·1 per cent and patches in 53·7 per cent of cases.

At 30 days, there were 2 (1·9 per cent) deaths; there were 4 postoperative CVAs (3·7 per cent), two of which had a disabling deficit. Analysis showed no significant increased risk for combined death/stroke with contralateral occlusion compared with non-occluded contralateral carotids ($\chi^2 = 0\cdot73$; P = n.s.).

Although the combined stroke/death rate of 5·6 per cent for contralateral carotid occlusions is higher than the rate for non-occluded contralateral vessels, this did not reach significance and the data suggest that the CVA risk is much less than previous studies have suggested. On the basis of the present data, operation for carotid stenosis with coexisting contralateral occlusion carries only a slight increase in risk for peroperative stroke and death.

Vascular 013

Surgery for carotid restenosis: a 13-year review

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Carotid artery restenosis is usually considered to be a benign process and the lack of symptoms is often attributed to the smooth surface of myointimal hyperplasia.

Between 1981 and 1994, 12 operations out of a total of 482 carotid endarterectomies (2·5 per cent) have been performed for carotid restenosis. All patients, but one, re-presented with amaurosis fugax. Operation findings, arteriogram reviews and histology were used to assess the pathology of the restenosis. The method of repair was determined principally by the pathology encountered at operation.

Results: *Median.

Method of repair	Time to re-operation (months*, range)	Pathology	Follow-up (months*)	Duplex Vel (m/s*)
Excision + V. graft ($n = 2$)	7 (5–9)	MIH	11·5	0·53
Vein patch ($n = 4$)	44 (10–108)	MIH/Ath/Th	30	0·94
Endarterectomy ($n = 3$)	132 (36–144)	Ath/Ca/Ulcer	80	1·82
Endart + V. patch ($n = 3$)	48 (22–144)	Ath/Th	52	0·92

MIH = Myointimal hyperplasia Ath = Atheroma Ca = Calcification Th = Thrombus

One patient required a vein patch for recurrent restenosis 10 months after an endarterectomy for primary restenosis where a thrombus was found covering an area of myointimal hyperplasia. One patient suffered a minor stroke and two patients have developed symptomless recurrent restenoses. Duplex scanning has shown a restenosis rate of 17 per cent of which 15 per cent cause symptoms. Bifurcation irregularity was seen on nine arteriograms.

Carotid restenosis may not be the benign self-limiting condition that is often suggested.

Vascular 014

Three-dimensional computerised tomographic imaging of thoracic outlet syndrome

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Symptoms of thoracic outlet syndrome (TOS) are related to congenital abnormalities which lead to abnormal compression or irritation of the subclavian artery, vein or brachial plexus. Successful treatment of TOS requires the management of both the muscular and osseous components. Investigations which assist in the diagnosis of TOS rely on arteriography, venography and nerve conduction studies. It would be desirable, though, to have preoperative information on the role of each of the soft and hard components of TOS to aid planning of the operation and the optimal choice of approach.

We report a series of ten patients in whom helical computerised tomographic (CT) scanning was performed. The studies were done with 3-mm sections reconstructed to 1-mm slices, following the infusion of 100 ml of contrast agent. The scans were repeated in the abducted position. The dataset was later analysed using a 3-dimensional (3D) surface rendering package, allowing accurate visualisation of the bony and vascular anatomy of TOS.

The results of this study show that the soft tissue component may be equally important as osseous compression of the neurovascular bundle in TOS, and that 3D reconstruction from helical CT scans is therefore a very useful adjunct to conventional methods of investigation of this condition.

Vascular 015

Does poor vein quality lead to intimal hyperplasia and graft stenosis?

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Poor vein quality has been associated with graft failure and stenosis in previous studies. In this study the link between vein morphology, neointimal hyperplasia and graft stenosis was analysed both *in vitro* and *in vivo*.

Segments of long saphenous vein from 100 patients undergoing arterial surgery were cultured for 14 days in medium containing 30 per cent fetal calf serum. Following fixation, the thickness of the neointimal layer that had developed during culture was measured. This was correlated with the original, preculture, vein wall intimal thickness measured on control sections. A further 46 segments of vein were taken from patients undergoing lower limb bypass. These were fixed and intimal thickness quantified as above. All 46 grafts entered a duplex scan surveillance programme to detect graft stenoses with a median follow-up of 12 months.

The median (range) intimal thickness was 45 (3–281) µm in the 100 veins before culture. There was no correlation however between this and the subsequent development of neointimal hyperplasia in culture (Pearson's r = 0·12). Seventeen of the 46 grafts (37 per cent) developed a stenosis. The median (range) intimal thickness in grafts developing a stenosis was 28 µm (7–140) compared to 19 µm (3–145) in grafts without a stenosis (P = 0·09, Mann–Whitney U).

In conclusion, the *in vitro* and *in vivo* evidence from this study does not support the hypothesis that pre-existing vein wall thickening is a key factor in the aetiology of vein graft stenosis.

Vascular 016

Outpatient clinic rapid evaluation of varicose veins by different Doppler techniques: accuracy compared with duplex scanning

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Hand-held Doppler ultrasound examination of primary varicose veins was compared with duplex scanning in a prospective, single-blind study. The veins of the popliteal fossa and the long saphenous vein (LSV) were assessed by different Doppler ultrasound methods in accord with a protocol, in busy clinics. Duplex scanning was done later. There were 87 symptomatic limbs in 61 patients (38 female: age 18–88, mean 53).

Doppler testing detected popliteal fossa reflux in all but 4 per cent of cases with short saphenous (SSV) reflux, and 8 per cent with popliteal (deep) vein reflux. As expected, it did not differentiate between these in all cases, but duplex scanning would have been requested in normal practice to make this distinction.

The accuracy of Doppler ultrasound tests for LSV reflux is shown in the Table:

	Percentage correct by hand-held Doppler ultrasound examination			
	At groin	10 cm below groin	Tapping test	Trendelenberg
Duplex reflux	94 per cent	86 per cent	83 per cent	85 per cent
Duplex no reflux	74 per cent	78 per cent	61 per cent	79 per cent

Doppler testing is a good screening method for popliteal fossa reflux, selecting limbs for duplex scanning to differentiate SSV and popliteal vein incompetence. For the LSV, a variety of Doppler tests all achieve reasonable accuracy, but at the expense of false positives, especially the tapping test. These standards can be achieved by rapid examination in busy outpatient clinics.

Vascular 017

The effect of reperfusion and sICAM-1 on neutrophils

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Introduction: Interaction between the CD11b receptor on neutrophils (PMNs) and intercellular adhesion molecule-1 (ICAM-1) on the endothelium is a prerequisite for neutrophil-mediated injury. Soluble ICAM-1 is shed from damaged endothelium.

Aims: To determine the effect of reperfusion plasma on PMN integrin expression and adhesion, and to examine the effect of sICAM-1 on adhesion.

Fifteen patients with a median age of 68 years undergoing elective aortic aneurysm repair were studied. Plasma was taken from the inferior vena cava following release of the aortic cross-clamp. PMNs were obtained from healthy volunteers and incubated in (i) culture medium, (ii) preoperative plasma and (iii) reperfusion plasma +/– various concentrations of sICAM-1. CD11b expression was measured using flow cytometry and adhesion using a gelatin-based adhesion assay.

Results: Medians and interquartile ranges were analysed using non-parametric stastistics. * P = ns, ** P<0·01.

		% PMN adhered				
		sICAM conc^{n} (ng/ml)				
Plasma type	CD11b	0	0·4	41·5	415	4150
Control	*15·1	**12·5	10·5	11·5	12·0	11·25
Before operation	14·5	14·5				
Reperfusion	*15·9	**56·5	40	32·5	22	15

Conclusion: An increase in PMN CD11b expression is not required for PMN adhesion. sICAM-1 decreased PMN adhesion in a dose-dependent manner. This study provides an insight into neutrophil adhesion and a potential physiological and therapeutic role for sICAM-1.

Vascular 018

Total antioxidant capacity in vascular patients

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Antioxidant defence systems protect the body from free radicals released during ischaemia-reperfusion (I/R). They are associated with the development of the I/R syndrome and sepsis.

Aims: To examine lipid peroxidation caused by free radicals and the total antioxidant capacity of patients with chronic critical leg ischaemia undergoing femoro-distal bypass.

Fifteen patients, 9 men and 6 women with a median age of 71 years, and 10 controls similarly matched were studied. Blood was taken preoperatively and assays performed for malondialdehyde (MDA), a product of lipid peroxidation, and total antioxidant capacity (TAC). Clinical outcome in terms of sepsis and the systemic inflammatory response syndrome (SIRS) were recorded.

Results: These are expressed as medians and interquartile ranges and analysed using a Mann–Whitney U-test. $^{*}P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$, $f\ P < 0{\cdot}01$.

	n	MDA μmol/l	TAC μmol/l
Non-SIRS	9	0·5 (0·34–0·76)*	1130 (990–1650)
SIRS	4	1·4 (0·85–1·59)**	490 (440–740) *f*
Controls	10	0·25 (0·02–0·68)*,**	860 (730–890) *f*

Conclusion: Vascular patients have an increased lipid peroxide concentration. Those patients who progress to inflammatory complications following surgery have preoperatively low TAC. This may provide a mechanism for identifying 'at risk' patients and it should be possible to augment their defence with exogenous antioxidants.

Vascular 019

Changes in aorto-iliac reconstruction – a seven-year audit

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A prospective audit of all vascular procedures in one unit was performed between 1988 and 1994. The results were analysed to assess whether any change in vascular procedures for aorto-iliac disease had occurred within this time. Vascular grafts companies were approached to ascertain whether the trends found in our audit were reflected at a national level.

	1988	1989	1990	1991	1992	1993	1994
ABFG	17·9%	22·8%	18·8%	13·5%	6·5%	3·6%	0·7%
ExAn	2·6%	2·6%	0·7%	7·7%	3·6%	14·6%	20·6%
Total	78	114	144	156	139	137	141

ABFG = Aorto-bifemoral graft, ExAn = Extra-anatomical graft
Total = Total vascular surgical procedures

From 1988 to 1994 there was a large increase in the numbers of iliac artery angioplasties. However, this made no impact on the proportion of vascular patients requiring aorto-iliac reconstruction. In these patients the aorto-bifemoral graft has been virtually replaced by the extra-anatomical graft. Sales figures of vascular grafts suggest that this trend is repeated nationally.

Moy 001

Results of kidney transplantation from asystolic cadveric donors

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Whilst the number of patients on the kidney transplant waiting list continues to rise, the pool of kidney donors in the UK has fallen in recent years. In an attempt to address this problem a non-heart beating donor (NHBD) organ retrieval programme has been established and the results over the first 3 years are presented.

Asystolic donors were referred from two sources: patients dying following failed attempts at resuscitation in the Accident and Emergency (A&E) department (n = 20) and ward-based patients who died as a result of catastrophic intracerebral haemorrhage (n = 4). After death, *in situ* kidney perfusion and cooling were achieved using an intra-aortic, double balloon, triple lumen catheter inserted via a femoral artery cut down. In the A&E setting a mechanical cardiorespiratory resuscitator was used to continue cardiac massage and ventilation until the initiation of *in situ* perfusion. The maximum acceptable period without cardiac massage (absolute warm ischaemic time) was 40 minutes. The programme resulted in 44 kidneys being retrieved over the 3-year period. Thirty NHBD kidneys were transplanted locally, 8 were used in other UK centres and 6 kidneys were not used. The median (95 per cent CI) warm and cold ischaemic times were 25 (20–29) minutes and 16·5 (14·6–18) hours respectively. Donor ages ranged from 25 to 63 (median 48) years. Postoperative dialysis was required in all patients for a median interval of 22 days (range 7–63). Twenty-six transplants (87 per cent) functioned with four primary non-functions (13 per cent). The median (95 per cent CI) serum creatinine at 24 months was 231 (169–302). There has been one graft failure due to rejection and one death with a functioning graft. Actuarial 1- and 2-year graft survival rates were 80 and 73 per cent respectively. During the period under study, 140 kidney transplants were performed in this unit and NHBD organs accounted for 21 per cent of our total programme. In conclusion, NHBD kidneys yield acceptable renal function and graft survival at two years follow-up; they have proved a valuable additional source of transplant kidneys.

Moy 002

The influence of different collagenase distension solutions and the timing of their delivery upon porcine islet isolation

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Cold pancreas storage and the use of University of Wisconsin (UW) solution are deleterious to the collagenase digestion of human pancreata. The aim of this study was to determine the influence of cold pancreas preservation and the intraductal delivery of collagenase in either UW, or University of Leicester (UL) solution upon porcine islet isolation. Forty pancreata were randomised between collagenase delivery in UW, or Hanks (control), both prior to and after a period of 60 minutes cold storage in citrate solution. Collagenase was also administered in UL solution, but only prior to cold storage. All pancreata were digested using an automated method using the same batch and concentration of collagenase.

The results are summarised below.

Timing	After cold storage		Before cold storage			
Collagenase Solvent	Hanks ($n = 8$) (standard)	UW ($n = 8$)	Hanks ($n = 8$)	UW ($n = 8$)	UL ($n = 8$)	P value*
No. islet EQ† g^{-1}	6924	8028	13672	21524	19814	0·02
Vol islet tissue $mm^3 g^{-1}$	3·55	4·53	7·14	11·02	10·15	0·02
Mean vol of an islet $\times 10^{-4} mm^3$	5·18	4·10	7·00	6·28	7·74	0·4
Per cent exocrine contamination	24·00	19·50	10·00	16·50	9·50	0·3
Insulin release $uIU/islet^{-1}/H^{-1}$	58·20	30·40	83·60	71·30	73·80	0·4

Median values. *Kruskall Wallis one-way analysis of variance. †Porcine islet EQ (80 μm).

We conclude that porcine islet yields can be significantly improved for xenotransplantation by the intraductal delivery of collagenase in UW immediately after pancreas excision and before cold storage, when compared to the standard method (P = 0·04).

Moy 003

Early increased platelet-activating factor and interleukin-8 in trauma patients at high risk for multiple organ failure

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We have previously shown early priming and activation of neutrophils in trauma patients at high risk for multiple organ failure (MOF). Our basic work showed that platelet-activating factor (PAF) and interleukin-8 (IL-8) are important mechanisms of neutrophil priming and activation. We therefore hypothesised that patients at high risk for MOF after trauma will have early increased plasma levels of PAF and IL-8.

We studied 33 high-risk trauma patients by sampling blood at 3, 6, 12 and 24 hours after injury. Patient plasma was incubated with donor neutrophils to assess priming (superoxide release in response to 1 μM *N*-formyl-methyl-leucyl-phenylalanine). Neutrophils were then pretreated with a PAF antagonist, WEB 2170, to inhibit plasma priming. Plasma IL-8 (in pg/mL) was determined with an ELISA. Data are mean ± SEM, and comparisons by a *t*-test.

Plasma sampled at 3, 6, 12 and 24 hours after injury primed donor neutrophils, compared to control plasma ($P < 0·05$). WEB 2170 inhibited the priming by plasma sampled at 3 hours after injury by 63·8 ± 7 per cent ($P < 0·01$). Plasma IL-8 was elevated at 6 (785 ± 183) and 12 (836 ± 175) hours after injury. Interestingly, IL-8 levels in MOF patients were 2½ times greater than non-MOF patients at 12 hours after injury (MOF = 1666 ± 622, non-MOF = 656 ± 150, $P < 0·01$).

Plasma priming at 3 hours after injury is mediated by PAF. This is followed by increased IL-8 at 6 and 12 hours, which corresponds to plasma priming and differentiates MOF and non-MOF patients. The sequential release of PAF and IL-8 after trauma may be important mechanisms of MOF.

Moy 004

Detection of circulating tumour cells and nodal metastases by reverse-transcriptase-polymerase chain reaction technique

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Detection of occult metastases in lymph nodes or of circulating tumour cells requires a novel sensitive technique. We have recently reported that CD44 gene activity is severely deranged in colorectal cancer cells. By amplifying the products of the CD44 gene using the reverse-transcriptase-polymerase chain reaction (RT-PCR), we have developed a novel technique for the detection of tumour cells in blood and lymph nodes. Peripheral or mesenteric blood (n = 24) and regional lymph nodes (n = 13) were obtained from patients with colorectal cancers. Total RNA was extracted and complementary DNA was synthesised with a viral enzyme. Any CD44-related cDNA was then amplified by PCR. Gel electrophoresis and blot hybridisation demonstrated many alternatively spliced bands, characteristic of tumour cells, in lymph nodes from 5 patients. Conventional staining confirmed the presence of metastatic cells in these lymph nodes. Four patients had abnormal CD44 gene expression in their blood, suggesting the presence of circulating tumour cells. In experimental studies, we demonstrated that the assay was sufficiently sensitive to detect 10 tumour cells per 10^6 leucocytes. As new therapies of cancer evolve, a sensitive technique for detecting tumour cells in blood or occult nodal metastases may be useful in monitoring patients following the surgical resection of cancer.

Moy 005

In vitro assessment of lipiodol targeted radiotherapy for primary and metastatic liver cancers

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Intra-arterial Lipiodol has been used to deliver targeted therapies to primary and some metastatic liver cancers, by substituting some of the iodine in Lipiodol with I^{131}. Early clinical results are encouraging, but the variable response may partly depend on local pharmacokinetics.

This study evaluated the *in vitro* cytotoxic effects of Lipiodol-I^{131} on human cell lines of hepatocellular carcinoma (Hep-G2), colorectal metastatic cancer (SW620), colorectal hepatic cancer (LoVo) and human umbilical vein endothelial cell (HUVEC) cell lines. Following exposure to Lipiodol-I^{131} for 48 hours, cell count and viability were assessed by haemocytometer, trypan blue, S-Rhodamine uptake and radioactivity assay. The effects of exposure to cold Lipiodol, Lipiodol-I^{131} (10, 20 or 40 µCi per ml) and radio-iodine^{131} alone were evaluated.

	Hep-G2 cell line Mean count (CPM) [gamma counter]	**Hep-G2 cell line** Mean cell counts [haemocytometer]	**HUVEC cell line** Mean count (CPM) [gamma counter]	**HUVEC cell line** Mean cell counts [haemocytometer]
Four per cent Lipiodol control	211·7 *(34·5)*	41·3 × 10^3 (*7·1*)	176·4 (*29·6*)	39·4 × 10^3 (*4·6*)
Plain I^{131} (40 µCi/ml)	365·2 *(26·7)*	38·1 × 10^3 (*3·8*)	375·9 (*19·9*)	44·4 × 10^3 (*2·1*)
Lipiodol-I^{131} (40 µCi/ml)	17 362 *(47·2)*	4·0 × 10^3 (*1·5*)	49 023 (*36·8*)	12·8 × 10^3 (2·2)

CPM = counts per minute. Values in parentheses are s.d.

There was a marked reduction in cell growth and cell viability of all the cancer cells following exposure to Lipiodol-I^{131}. The effects the on Hep-G2 cell line were very similar to those on other cancer cell lines (SW620 and LoVo). There were no cytotoxic effects following exposure to Iodine^{123} alone in any of the cell lines (malignant and non-malignant). This study showed that there was a marked cytotoxic effect by the Lipiodol-I^{131} on all the cancer cell lines. There was no difference between the control wells and the Iodine^{131} alone. This confirms that effective Lipiodol-I^{131} targeted therapy is dependent on the uptake and retention of Lipiodol by liver cancer cells, and appears to be a specific phenomenon.

Moy 006

Increased intestinal permeability in obstructive jaundice is reversed by internal biliary drainage

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Gut mucosal barrier dysfunction is implicated in the pathophysiology of complications in patients with obstructive jaundice (OJ). This study investigates the effect of OJ on intestinal permeability and bacterial translocation, and examines the effect of internal biliary drainage.

Methods: *Animal study.* Wistar rats underwent bile duct ligation (BDL) (n = 12) or sham operation (n = 12). Intestinal permeability was assessed using ^{14}C polyethylene glycol 4000 preoperatively and at 7 days postoperatively. Bacterial translocation was also measured.

Clinical study. Intestinal permeability was measured, using the lactulose/mannitol absorption ratio in 33 patients with OJ preoperatively, and at 1, 7 and 28 days after internal biliary drainage (surgical, endoscopic or percutaneous), and in 6 non-jaundiced controls.

Results: *Animal study.* Mean percentage change in permeability following operation was signifciantly different between the two groups [+66·2 per cent (BDL) vs −11·6 per cent (Sham), $P < 0·01$]. Significant bacterial translocation also occurred [58 per cent (BDL) vs 0 per cent (Sham), $P < 0·01$].

Clinical study. The lactulose/mannitol ratio was significantly increased in patients with OJ (0·050) compared to controls (0·010) prior to therapeutic intervention ($P < 0·005$). Following internal biliary drainage, the lactulose/mannitol ratio returned to normal by day 28 ($P < 0·01$).

Conclusions: These data support the hypothesis that OJ results in gut mucosal barrier dysfunction, which is reversed by internal biliary drainage. Improving gut barrier function may be important in preventing septic and other complications in OJ.

Moy 007

Peritoneal cytology in the surgical evaluation of gastric carcinoma

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The majority of patients who have 'curative' surgery for advanced carcinoma of the stomach will develop disseminated peritoneal metastases. The Japanese have shown the presence of free malignant cells in the peritoneum to be associated with a decreased survival, yet this phenomenon has received little attention in the West. The aim of this study was to evaluate the role of peritoneal cytology in patients with gastric carcinoma.

In a two-year period, peritoneal cytology samples were obtained during surgical evaluation of 89 patients with gastric adenocarcinoma. Tumour staging followed JRSSC† guidelines. The surface area of any serosal penetration by tumour was measured. No patient with an intact serosa had free malignant cells, but 23 (36 per cent) of 63 patients with macroscopic evidence of serosal penetration proved positive. All eight patients with ascites had positive cytology. Patients with positive cytology had a greater area of serosal penetration than those with negative cytology (median 11·5 vs $5{\cdot}5\,\text{cm}^2$; $P < 0{\cdot}05$, Mann–Whitney test). Survival at a mean 24 months follow-up was 22 per cent and 66 per cent for cytology-positive and cytology-negative patients respectively (Chi-squared = 12·15, $P < 0{\cdot}001$).

The study confirms that free peritoneal malignant cells can be identified in patients with advanced gastric cancer. Malignant cells are not seen prior to serosal penetration and the likelihood of positive cytology increases along with area of serosal penetration. Positive cytology is associated with a reduced life expectancy. Few patients with advanced carcinoma of the stomach are cured by surgery alone; analysis of peritoneal cytology is simple to perform and may have a role in the selection of patients for adjuvant therapy.

†Japanese Research Society for Stomach Cancer.

Moy 008

Vein graft stenosis and heparin responsiveness of human vascular smooth muscle cells

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The mechanism underlying myointimal hyperplasia (MIH), the commonest cause of stenosis after arterial intervention, is poorly understood. It has been demonstrated that cultured human vascular smooth muscle cell (VSMC) resistance to the growth inhibitor heparin is consistent within individuals and strongly predictive of the subsequent development of vein graft stenoses. The aim of this study was to examine the cellular basis of heparin resistance by analysing human VSMC heparin binding.

A group of 13 patients was followed in our standard graft surveillance programme based on serial Duplex scanning for 1 year, with stenoses being confirmed by angiography. Seven patients developed significant stenoses (> 50 per cent reduction in luminal diameter) within the follow-up period. Heparin resistance was assessed by increase in cultured human VSMC number over 14 days in response to 15 per cent fetal calf serum +/– 100 µg/ml heparin. Maximum heparin binding was assayed by exposing the cells to tritiated heparin at 4°C for 30 minutes.

These results demonstrated that maximum heparin binding is significantly correlated with inhibition of proliferation ($r = 0{\cdot}81$; $n = 13$; $P < 0{\cdot}001$, two-tailed t-test). Furthermore, reduced binding is also significantly correlated with graft outcome (point-biserial coefficient $r = 0{\cdot}651$; $n = 13$; $P < 0{\cdot}05$).

It can be concluded that heparin binding by human VSMC is associated with both proliferative responses and graft outcome, and is the first biological marker for stenosis to be identified. These observations may lead to a rational and effective management of an important clinical problem, including the prospect of identifying individuals at increased risk of graft failure and potentially modifying the outcome.

Lower Gastrointestinal 11–16 Thursday 23 May, 16·30–17·30

LGI 011

The role of the nurse endoscopist in colorectal practice

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Screening initiatives relating to colorectal disease have gained in momentum. Demand for sigmoidoscopy and endoscopist skills have risen. Units are exploring the use of the nurse endoscopist to meet these demands. This paper discusses the training and assessment of nurse endoscopists.

A nurse practitioner was trained to perform diagnostic flexible sigmoidoscopy utilising a local protocol approved by the Ethics and Research Committee and supervised by an experienced consultant surgeon.

During training 50 sigmoidoscopies were observed. Twenty-five withdrawals and 25 full procedures under direct supervision and 50 indirectly supervised procedures followed. A training log was maintained.

The assessment consisted of the consultant and trainee performing 50 video-taped procedures each. The endoscopist performing each procedure was unidentified. Tapes were reviewed and scored by an independent assessor. An assessment form with scoring system was utilised to mark each procedure for duration, depth, level, quality and diagnosis. The nurse was deemed competent if her assessment score was within 15 per cent of that of the consultant trainer.

Results showed that a nurse endoscopist could achieve the level of competence and skill required to contribute effectively to direct access, screening and routine sigmoidoscopy services. Technical assessment should be utilised to confirm competence and audit the nurse endoscopist progress.

LGI 012

Prospective evaluation of the training and practice of a nurse flexible sigmoidoscopist

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The introduction of flexible sigmoidoscopic screening for colorectal cancer would overwhelm the medical endoscopy service. This study represents the initial investigation into the results of the first ENB recognised nurse endoscopy service in the UK.

The nurse was trained in four stages. Stage 1: visuospatial orientation on a colon model and observation of 35 sigmoidoscopies. Stage 2: supervised withdrawal of the sigmoidoscope in 35 patients. Stage 3: supervised performance of 35 examinations. Stage 4: independent practice with a consultant endoscopist on site but not directly supervising the procedure. Endoscopies were video-recorded and reviewed by a consultant endoscopist and every patient also underwent barium enema examination.

Eighty-seven independent flexible sigmoidoscopies have now been performed. The mean duration of the examinations was 10·5 minutes and the mean length of colon examined was 52·2 cm. The examination was considered incomplete in 17 patients due to discomfort ($n = 3$), inadequate preparation ($n = 9$) or stricture ($n = 5$). Thirty-eight of the completed examinations were normal. No pathology was missed by the nurse endoscopist. The results of the abnormal examinations are shown below:

Pathology	Diverticular disease	Benign polyps	IBD	Cancer
Number	21	21	7	3

We conclude that, with adequate training, a nurse endoscopist is able to provide a safe and efficient flexible sigmoidoscopy service.

IBD = Inflammatory Bowel Disease, ENB = English National Board

LGI 013

Wessex colorectal cancer audit: emergency referrals

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A population-based prospective audit on all patients with colorectal cancer has completed recruitment in the Wessex region (population 3·1 million). Of 4887 patients diagnosed with colorectal cancer between September 1991 and August 1994, 1190 were referred to hospital as an emergency. 1027 (86·3 per cent) had surgery, and this was performed by a consultant in 357 (34·8 per cent) of cases. 729 (71·0 per cent) underwent resection with restoration of intestinal continuity, and 118 (16·2 per cent) of these had a proximal diversion. In 410 (39·9 per cent) the procedure was regarded as curative by the surgeon, although this was not recorded in 199 (19·4 per cent) of cases. Four hundred and forty-one patients (42·9 per cent) suffered a postoperative complication and 165 (16·1 per cent) died within thirty days of surgery. The mean length of stay in hospital was 19·3 days (median 15 days), and 146 (14·2 per cent) of patients spent a mean of 4·5 days in an intensive-care or high-dependency unit.

Consultants performed significantly fewer emergency than elective procedures compared to higher surgical trainees (357/2248, 15·8 per cent vs 564/1588, 35·5 per cent). Late-stage disease was present in 56·2 per cent of cases referred as emergencies compared to 46·1 per cent of elective cases (P = 0·00). The 30-day postoperative mortality (16·1 vs 4·8 per cent) and postoperative complication rate (42·9 vs 32·9 per cent) were higher for emergency referrals compared to elective referrals. The postoperative mortality for emergency referrals was lower following procedures performed by consultants than surgical trainees (11·1 vs 18·5 per cent, χ^2 = 9·78, P = 0·020).

These data suggest that results from surgery for emergency referrals with colorectal cancer has a poor outcome compared with elective cases. Additional resources are required to provide patients with optimised care. This should include provision for more day-time operating.

LGI 014

Wessex colorectal cancer audit: anastomotic leakage following elective anterior resection

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A population-based prospective audit of colorectal cancer has completed recruitment in the Wessex Region (population 3·1 million). Between September 1991 and August 1994 1474 cases of rectal cancer were diagnosed. Ninety per cent of patients underwent an operation of which there were 603 elective anterior resections. Major anastomotic leakage occurred in 33 cases (5·5 per cent) and minor leakage in 23 cases (3·8 per cent). Retrospective analysis of various factors showed the use of a defunctioning colostomy and the surgeon's experience of rectal surgery to be most significant.

The presence of a defunctioning colostomy reduced the frequency of anastomotic leakage from 11·4 per cent to 6·5 per cent (χ^2 = 4·10, P = 0·043). Re-operation was required more frequently where there was no proximal diversion (7·3 per cent of 3·0 per cent, χ^2 = 5·07, P = 0·0024). Postoperative mortality was greater following a leak, where no diversion was in place (10 per cent of 4·1 per cent, χ^2 = 4·29, P < 0·005).

Surgeons who performed ten or more operations on rectal cancer per year had a significantly lower leak rate (6·9 per cent) than those who performed less (14·1 per cent, $\chi^2 = 8{\cdot}01$, $P = 0{\cdot}0047$). The more experienced surgeons used proximal diversions more frequently (49·6 per cent of 30·0 per cent, $\chi^2 = 20{\cdot}6$, $P < 0{\cdot}00$).

These data suggest that proximal diversion reduces both the frequency and consequences of anastomotic leakage following anterior resection. More experienced colorectal surgeons use more proximal diversions and have lower leak rates.

LGI 015

Standards of care are not being met: Wessex colorectal cancer audit

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Standards of care were developed by an expert working group and implemented throughout Wessex. The 31 standards covered the areas of information recorded, diagnostic and preoperative investigations, referral, pathology, surgery and outcome. The standards have been assessed on 4980 cases of primary colorectal cancer diagnosed between September 1991 and August 1995.

There are 13 standards met by all hospitals, 6 other standards were not met in any hospital. These latter standards concern referral times and the recording of family history, height of the anastomosis, ASA grade and length of tumour.

Over the three-year period of audit, 26 standards were met or demonstrated an improvement by treatment centre, 4 demonstrated no change and 2 standards deteriorated. The latter were concerning the proportion of cases having a preoperative X-ray, and the proportion of patients operated upon within 28 days of their first outpatient appointment.

An effective mechanism for improving patient care through the development and subsequent monitoring of performance against locally set, practical standards has been evolved. The colorectal specialists who set these standards must now focus on those consistently not met and ask why.

LGI 016

How valuable is the small bowel follow-through examination in adults?

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Contrast examinations consume a large amount of resources and are often normal. The diagnostic yield and indications for small bowel constrast studies are uncertain. Therefore 100 consecutive barium small bowel follow-through examinations were audited. Three case notes were unobtainable (2 had normal results), 2 examinations were unsuccessful and 15 in children were excluded. The remaining 80 were in adults of mean age 47 years (range 15–84, 47 (59 per cent) female). The indications were assessment of known Crohn's disease (14, 18 per cent) or volvulus (1, 1 per cent), diarrhoea and pain (56, 70 per cent) and bleeding (9, 11 per cent).

Excluding patients with known small bowel disease, 65 examinations were performed for diagnostic reasons. Only 3 (5 per cent) identified Crohn's disease, the remainder were either normal (60, 91 per cent) or showed insignificant abnormalities (2, 4 per cent).

Sixty-two patients had normal or insignificantly abnormal results, 30 (46 per cent) were discharged immediately, 21 (32 per cent) observed, and 10 (15 per cent) investigated further, resulting in the diagnosis of colonic carcinoma, appendix mucocele, duodenal ulcer and colonic polyp. In the remainder the ultimate diagnosis was unspecified or ascribed to irritable bowel syndrome. In the absence of specific indications a follow-through examination rarely reveals pathology and is often unnecessary.

Breast 11–16

Thursday 23 May, 16·30–17·30

Breast 011

Presentation and diagnosis of breast cancer in women under 40

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Recent reports suggest breast cancer is commonly misdiagnosed in younger women, often leading to litigation[1], and mammography is an insensitive diagnostic tool in this age group. A retrospective review of 79 new cases of breast cancer diagnosed in women under 40 in one hospital between 1985 to 1994 was performed to assess the mode of presentation and diagnosis.

Sixty-two per cent of women presented with a painless lump and a further 25 per cent presented with a lump with associated pain or discomfort. Only 11 per cent had a 'typical' symptom of malignancy such as skin tethering, nipple discharge or indrawing of the nipple. 15 per cent of women had a significant family history for breast cancer.

Fine needle aspirates were carried out on all but one of the women and were suspicious or diagnostic of malignancy in 85 per cent.

Mammograms were carried out on 52 of the 79 women and only 65 per cent showed changes suspicious or suggestive of malignancy. The other 35 per cent were reported as definitely or probably benign.

We have now compared MRI, mammography and ultrasound prospectively in a cohort of 24 women with breast cancer and have found that MRI detected mutifocal breast cancer in 21 per cent of women when other imaging modalities failed. The use of MRI in detecting malignancy in younger women with breast symptoms needs further evaluation.

[1] Physician Insurers Association of America, Breast Cancer Study 1995.

Breast 012

Hormone replacement therapy-induced mastalgia responds to evening primrose oil

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Breast pain affects 70 per cent of premenopausal but only 10 per cent of postmenopausal women. The incidence of mastalgia during hormone replacement therapy (HRT) is unknown. In a prospective study, women starting HRT in a menopause clinic were questioned about breast symptoms. Forty-two women then kept a breast pain diary for the first three months of HRT. Women with > 7 days of breast pain for at least one cycle were defined as likely to benefit from mastalgia therapy.

Before treatment 14 (33 per cent) of women complained of mastalgia compared to 27 (64 per cent) after 3 months of HRT ($P < 0{\cdot}01$). 59 per cent of women developing pain on HRT had more than 7 days of breast pain. More women with prior breast pain (10/14) redeveloped pain on HRT ($P < 0{\cdot}05$), and had the most severe symptoms. No significant difference was found between women on oestrogen only therapy and those on combined HRT for number of HRT cycles with pain or number of women with mastalgia. Ten women with HRT-induced mastalgia were treated with evening primrose oil, 2 g/day and 7 improved symptomatically assessed by reduced breast pain score. Mastalgia is common on HRT and women should be warned to expect pain.

HRT induced breast pain responds to evening primrose oil.

Statistics: χ^2 test.

Breast 013

A randomised trial of drain management after breast cancer surgery

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Seromas are common following breast surgery with axillary clearance, and suction drainage reduces this incidence. Some believe seromas are more common if drains are removed too early, and traditionally patients stay in hospital until drainage becomes minimal. We aimed to determine whether axillary drains can be safely removed and patients allowed home after 5 days.

Over a 3-year period, 120 patients (median age 61 years, range 29–83) undergoing Patey mastectomy ($n = 90$) or wide local excision with axillary clearance ($n = 30$) entered a prospective randomised trial, comparing axillary drain removal at 5 days (group 1) with drain removal when drainage decreased to < 30 ml/day (group 2). Where possible patients were discharged at 5 days.

A seroma requiring aspiration occurred in 29 per cent (17/59) of group 1 and 25 per cent (15/61) of group 2 (NS). There was no significant difference in wound infection (8 per cent vs 5 per cent) or postoperative lymphoedema (8 per cent vs 11 per cent) between the groups. A follow-up questionnaire revealed that 81 per cent of patients preferred early drain removal followed by outpatient seroma aspiration if necessary, including 84 per cent of patients who actually developed seromas.

We conclude that it is safe and acceptable to remove drains and allow early discharge following breast cancer surgery with axillary clearance.

Breast 014

Conservative management of acute mastitis and breast abscesses after ultrasound assessment

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Breast abscesses are conventionally treated by incision and drainage. An alternative to surgery is aspiration of pus combined with antibiotic therapy. Our current practice for a suspected breast abscess is a preliminary ultrasound scan, aspiration of any pus, antibiotic therapy and repeat aspiration in the outpatient clinic if necessary. Inflammatory masses are treated with antibiotics alone. To assess this strategy, a retrospective review was carried out to compare the outcome in patients undergoing aspiration against other treatment regimes used during the same study period, by other surgical teams within our hospital.

Over a two-year period 53 patients were admitted to the acute surgical ward with a suspected breast abscess. Twenty-two abscesses were aspirated, of which 19 resolved and 3 required subsequent incision and drainage. Eight patients underwent primary incision and drainage of their abscess. In 5 patients the abscess discharged spontaneously before any intervention. The remaining 18 patients were found on ultrasound to have inflammation without focal pus formation. Of these, 16 settled on antibiotics, but one patient subsequently developed an abscess, and another had an inflammatory cancer.

These results suggest that the combination of diagnostic ultrasound and aspiration of pus is an effective strategy for the treatment of a suspected breast abscess. Such a strategy should enable almost all inflammatory episodes to be managed conservatively in the breast clinic.

Breast 015

First two years of a nurse practitioner-led follow-up breast clinic

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A breast follow-up clinic was established to be run independently by a breast nurse practitioner following a twelve-month training interval. The majority of patients attended for routine follow-up after surgery for breast cancer or repeat examination for benign breast disease. A few, usually relatives of breast cancer patients, were seen as direct referrals for general discussion and to be taught breast self-examination. Clear guidelines were produced for the conduct of the clinic which included that they could only occur when a consultant surgeon was working in an adjacent general surgical clinic, and that all patients were offered a consultation with him in addition if they preferred.

A total of 48 clinics were held. Some 231 clinic visits were recorded, median five patients per clinic (range 1–11). Nineteen booked patients failed to attend. Patients included: breast cancer follow-up (104), follow-up of benign, mostly fibrocystic disease (105), preoperative counselling for breast cancer (18) and breast self-examination tuition (4). A total of 136 (59 per cent) were seen by the nurse alone but the consultant surgeon was called to assist in the remainder. Procedures performed in the clinic included aspiration for cytology (7) or cyst (6) and Trucut biopsy (4). In follow-up, which ranges up to two years, no significant lesion has been missed in this group of patients.

The nurse practitioner clinic is a useful resource. It increases the throughput in surgical outpatients and is generally approved of by patients who see the same person at each visit instead of a new SHO each time. The nurse practitioner generally has more time available for counselling and can deal with problems such as breast prosthesis and lymphoedema at the same time. The clinic is an attractive option for follow-up of the majority of patients with breast disease.

Breast 016

The treatment of mammillary fistulas

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The management of mammillary fistulas (MF) is controversial. The outcome of 66 patients (with 76 mammillary fistulas) treated either by laying open of the tract (LT) or by total duct excision (TDE) over two 6-year periods was compared.

Patient ages were similar in the two groups LT and TDE [mean = 35·5 y (median = 36·0 y) vs mean = 36·0 y (median = 37·0 y) respectively]. Complications occurred in 20/49 (41 per cent) of MF treated by LT (14 recurrences, 6 wound complications), and 7/27 (26 per cent) MF treated by TDE (4 recurrences, 3 wound complications). The mean time for recurrence was 20 months (1–108) in fistulas treated by LT and 6·25 months in fistulas treated by TDE (1–18 months). Twenty-four of the 27 (89 per cent) complications occurred in cigarette smokers.

Periductal mastitis is strongly associated with cigarette smoking and affects the lactiferous ducts behind the areola. Mammillary fistulas are a complication of this disease and can be treated by laying open the tract or total duct excision. Laying open the fistulous tract gives a high recurrence rate (29 per cent) and total duct excision may be the preferred option.

Trans 001

Randomised controlled trial of three needle sizes for renal transplant biopsy

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The size and quality of the biopsy material are important factors in the interpretation of renal transplant histopathology. Needle core biopsy using a spring-loaded 'gun' has been shown to be safe and effective but a number of different needle sizes are available. The aim of this study was to examine the success and complication rate of three different needle sizes for renal transplant biopsy. A consecutive series of 100 renal transplant biopsies performed under ultrasound guidance were studied. Patients were randomised to undergo biopsy using either a 14, 16 or 18 gauge 'Bioptycut' needle. All histological material was examined by the same consultant histopathologist. The length and diameter of each biopsy were measured and the presence/absence of renal tissue, renal cortex and medulla and the number of glomeruli were recorded. The pathologist scored the diagnostic value of each specimen and the ease of use of each needle was graded by the operator. Post-biopsy pain was assessed using verbal response and linear analogue scales: 14G biopsy cores (n = 33) were longer than both 16G (n = 33) and 18G (n = 34) cores ($P < 0{\cdot}05$) and contained more glomeruli (mean number for 14, 16 and 18G = 14, 11 and 9 respectively). Scores for diagnostic usefulness were higher for 14G vs 16G ($P = 0{\cdot}04$), 14G vs 18G ($P = 0{\cdot}001$) and 16G vs 18G ($P = 0{\cdot}018$). There were no significant differences in the ease of use between the 14G, 16G and 18G needles. Post-biopsy pain scores were not different between the 3 groups using verbal response data but more pain was recorded for 14G vs 16G needles using a linear analogue scale ($P = 0{\cdot}025$). Macroscopic haematuria occurred in 8 patients (no significant differences between the 3 groups) and there were no other complications. All 3 needle sizes are safe for use in renal transplant biopsy but the larger needles provide more tissue, more glomeruli and are more useful diagnostically. A 14G needle may be associated with more pain and the 16G needle would appear to offer the best compromise between diagnostic usefulness and patient acceptability.

Trans 002

Teaching in the operating theatre – a consultant's assessment of his own performance

Richard Cobb *Birmingham Heartlands Hospital, Birmingham*

Much attention is paid now to trainees' log books in the assessment of training. However, there are few data illustrating the successes and failures of trainers.

For the first two years after appointment (1 May 1993 to 30 April 1995) all operations performed, supervised or observed by one consultant general surgeon were entered on to a database (Filemaker Pro on a Macintosh Powerbook). These data have been analysed to identify the numbers of operations performed by the consultant alone (C), by the consultant with trainee assisting (CTA), by the trainee assisted by the consultant (TAC), or by the trainee observed by the consultant (TOC).

A total of 835 operations were analysed for this 2-year study.

	C	CTA	TAC	TOC
Scheduled lists	293	274	109	89
Emergencies	10	38	15	7
Total	303	312	124	96

Factors that restricted opportunities for training in the operating theatre were:

1. Pressure of time in theatre.
2. Trainees dealing with emergency admissions during scheduled lists.
3. Locums.
4. A waiting list initiative.

In the absence of comparative data, I do not know whether I am a good or bad trainer. I present these data for the Fellows of ASGBI to comment (and judge).

Trans 003

Importance of thickness of skin grafts in preventing contraction

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Scar contracture is an unfortunate result of injury, particularly when there has been skin loss. Skin grafting reduces contraction; although thick grafts are effective, thin grafts give poor results. This means that the dermis is important in reducing contraction and the thickness of the dermis in the graft is critical. The reason for this is unknown.

The aim of this study was to document the effect of extracts of different levels of dermis on the ability of fibroblasts to cause contraction, using the fibroblast-populated collagen lattice (FPCL) as a model. Human dermis was split into 3 layers (superficial, middle and deep) by a Padgett's dermatome. Extracts were prepared from each layer using successive solvents (water, normal saline, 1M saline, citrate buffer and urea). Collagen lattices (n = 100) were prepared and seeded with fibroblasts. Each of the extracts (5) from each layer (3) was added to 5 of the lattices and 25 of the FPCLs were used as the control preparation.

The degree of contraction of the FPCL was measured daily for 4 days. The results showed that the citrated buffer extract was most effective in limiting contraction and that the extract of the deep dermis was more effective than extracts from the middle or superficial dermis [$P < 0{\cdot}001$ Bonferoni test ($r = 0{\cdot}943$)].

The results suggest that the inhibition of contraction by skin grafting is due to substances present in the dermis and these substances are present in greatest concentration in the deeper layer of the dermis. The nature of these substances is under investigation.

Trans 004

A prospective study of hepatobiliary scintigraphy and cholangiography for detection of early biliary complications after orthotopic liver transplantation

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Early biliary complications following orthotopic liver transplantation (OLT) with biliary duct to duct anastomosis without T tube were prospectively investigated by endoscopic retrograde cholangiography (ERC) and hepato-biliary scintigraphy (HBSc). Sixty-seven patients had both ERC and HBSc performed within 30 days after liver transplantation. Scintigraphy was performed using 150 MBq of Tc-99 Mebrofenin and reported by 2 observers as normal, leak, stricture or cholestasis and compared with ERC findings. The number of endoscopic and surgical biliary interventions performed within 3 months of transplantation were recorded.

Of the 45 patients with normal cholangiography, HBSc was reported as normal in 27, leak in 5, stricture in 11 and cholestasis in 2. HBSc diagnosed 7 of 14 biliary leaks and 5 of 8 biliary strictures seen on ERC (sensitivity 50 per cent and 62 per cent). Seven leaks and 15 strictures seen on HBSc were not confirmed by ERC (specificity 79 per cent and 64 per cent, respectively). None of the patients with normal scintigraphy required biliary intervention. Forty-three per cent of patients with biliary leaks and 35 per cent with strictures diagnosed on scintigraphy required interventional treatment. If both investigations reported leak or stricture, the intervention rate was 75 per cent and 40 per cent respectively. This study showed that scintigraphy under-reports the incidence of biliary complications seen on ERC. HBSc diagnosed both leaks and strictures in patients with a normal cholangiogram. Normal scintigraphy is unlikely to result in intervention. Biliary complications diagnosed by scintigraphy result in intervention in one-third of patients but if confirmed by ERC the intervention rate rises to two-thirds. HSC is a useful screening test for biliary complications which should be confirmed by cholangiography.

Trans 005

Heparin modulates endothelial cell immunogenicity

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Heparin has immunosuppressive activity in some models of allograft rejection. The first graft tissue to contact the recipient immune system following transplantation is the endothelium; this can express immunogenic class II major histocompatibility (MHC) antigens and the ICAM-1 adhesion molecule. During rejection the expression of these molecules is enhanced by the major proinflammatory cytokine interferon-γ (IFN-γ). The possibility that heparin inhibits the activity of IFN-γ was investigated in this study.

Human umbilical vein endothelial cells (HUVEC) were cultured. Compared with cells stimulated with IFN-γ in the absence of heparin, those stimulated with standard and a non-anticoagulant heparin derivative showed reduced expression of MHC Class II antigens ($P < 0{\cdot}001$). This was also observed when heparin sulphate and a low molecular weight heparin were used; no modulation was produced by chondroitin sulphate. ICAM-1 upregulation was smaller when HUVEC were stimulated with IFN-γ in the presence of heparin ($P < 0{\cdot}001$) and the adhesion between these HUVEC and allogeneic T cells was reduced ($P < 0{\cdot}05$). Furthermore, the proliferation of HUVEC-responsive T lymphocytes was decreased following HUVEC activation in the presence of heparin ($P < 0{\cdot}05$).

Heparin-like molecules antagonise the proinflammatory activity of IFN-γ and reduce endothelial immunogenicity. They may have the potential to supplement conventional immunosuppression following organ transplantation.

Trans 006

Work-load generated by setting up a non-heart beating kidney transplant programme

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A non-heart beating donor (NHBD) kidney transplant programme was set up 3 years ago in an attempt to improve local transplant numbers. This report describes the total work-load which has been generated by the programme. NHBDs were referred from 2 sources: the Accident and Emergency (A&E) Department (failed resuscitations following cardiac arrest) and ward patients dying from intracerebral haemorrhage. Donor selection criteria included age <60 years and warm ischaemic time <40 minutes. A rapid-response retrieval team was established consisting of 1 or 2 transplant co-ordinators and 1 or 2 surgeons. The local A&E department is not in the same hospital as the Transplant Unit and the team had to travel to all the referrals made. Organisation of a NHBD retrieval involves 5 stages: referral by appropriate clinicians and mobilisation of the team, obtaining consent from relatives, *in situ* kidney perfusion, referral to the coroner and transfer to an operating theatre for the retrieval procedure. Over a three-year period a total of 73 referrals have been made, 64 from the A&E department and 9 from the wards. Organ procurement was performed in 24 cases (33 per cent) and resulted in the retrieval of 44 kidneys. Reasons for failure to achieve organ procurement were: refused consent 13 (18 per cent), relatives unavailable to ask for consent 9 (12 per cent), technical problems with catheter insertion or perfusion 10 (14 per cent), transplant staff unavailable 1 (1 per cent), long asystolic period 8 (11 per cent) and donor unsuitable for other reasons 8 (11 per cent). Of the 44 kidneys retrieved, 30 were transplanted locally, 8 were transplanted at other centres in the UK and 6 were discarded or used for research because a suitably matched recipient could not be found. Locally transplanted NHBD kidneys represent 21 per cent of the total transplant programme during the time period under study. NHBD kidneys are a good source of additional organs for transplantation but only one-third of referrals result in a successful procurement procedure. The setting up of a programme is labour-intensive and requires a highly committed staff.

UGI 010

Multiple firing endoloops – a new treatment for varices

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Endoscopic variceal ligation appears more effective and safer than injection sclerotherapy in achieving haemostasis in bleeding oesophageal varices. A multiple firing band ligating device has been developed. We have previously reported that endoloops were significantly more effective than elastic bands in achieving haemostasis on vessels more than 2 mm in external diameter. A modified cap (endcap) for attachment to the tip of the endoscope has been developed to deploy the endoloops. This allows repeated firing of endoloops via the biopsy channel. Repeated firing has been performed on postmortem tissue ($n = 10$) and on porcine oesophagus ($n = 8$). Endoloops have been used on patients presenting with bleeding oesophageal varices ($n = 6$). All were placed without an overtube and with the patient receiving only midazolam sedation. No discomfort was reported from any patient following the application of the endoloops and complete haemostasis was achieved. Clinically there was no evidence of a rebleed and all patients were discharged from hospital. Endoloops remained attached for up to 3 weeks but had detached by 5 weeks.

The advantages of this new method over multiple band ligation are: (1) no restriction on the number of endoloops that can be deployed; (2) loading the endoloop is simple – by passage along the biopsy channel; (3) experimental models have shown the endoloop to be superior to elastic bands in achieving haemostasis in large vessels; (4) early studies in humans have shown it to be safe and effective.

UGI 011

The incidence of *H.pylori* after vagotomy for DU disease is dependent on the drainage procedure performed

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Background: Many patients who have been treated for duodenal ulcers (DU) by vagotomy present again for endoscopy with a variety of symptoms. The aim of this prospective study was to evaluate the incidence of *H.pylori* (HP) infection in these patients.
Method: Over a period of 18 months, 54 patients who had undergone vagotomy for DU were referred for endoscopy. Thirty-three had vagotomy and pyloroplasty (VP), 16 vagotomy and gastroenterostomy (VGE) and 5 highly selective vagotomy (HSV). A further 50 patients with non-operated DU disease were also endoscoped and were used as a reference series. The presence of HP was assessed by a urease-detecting CLO-test, on endoscopic antral biopsies.
Results: Endoscopy revealed antral gastritis in 76 per cent of patients, DU or duodenitis in 19 per cent (all associated with antral gastritis), no abnormality in 11 per cent, and other pathologies in the remaining 13 per cent. HP was detected in 52 per cent of patients following vagotomy, which was significantly lower than 93 per cent in the non-operated group ($P < 0{\cdot}001$). All patients with DU or duodenitis were HP-positive. The incidence of HP was significantly higher following VP than VGE (61 per cent vs 25 per cent; $P = 0{\cdot}02$) and it was found in 100 per cent of patients following HSV (ns). (Statistics: Fisher's exact test.)
Conclusions: (1) All patients with recurrent DU following vagotomy were found to be HP-positive. (2) Vagotomy was associated with a 50 per cent reduction in HP colonisation of the antrum. (3) The reduction in HP is procedure dependent, and may be related to bile reflux causing eradication of the organism. This suggests a mechanism to explain the relative recurrence rates following surgery for DU disease.

UGI 012

Screening for gastric cancer: is serology for *Helicobacter pylori* feasible?

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Helicobacter pylori has been implicated in the genesis of gastric neoplasia. We investigated the correlation between seropositivity for antibodies to *H.pylori* and gastric cancer in England to discover if this could be used as a screening procedure for dyspeptic patients.

Stored serum samples from 154 patients with confirmed gastric cancer were assayed for antibodies to *H.pylori*. The results were correlated with demographic data from the patients, histology of the tumours and the extent of spread of the tumours. Results were compared with sex and date of birth-matched, dyspeptic controls.

Seventy-seven per cent of cases were positive for *H.pylori* compared with 65 per cent of controls ($P = 0{\cdot}044$). Despite its association with intestinal type metaplasia, *H.pylori* was not related to the Lauren classification of the tumour. However, it was related to the tumour's site, being associated with tumours of the body and pylorus, but not with cancers of the cardia ($P < 0{\cdot}05$).

In an age group where stomach cancer is common, screening by means of antibody assays to *H.pylori* would miss a quarter of these tumours. Also, since tumours of the cardia are increasing in incidence and these appear unrelated to *H.pylori*, it is likely that even more tumours would be missed in the future.

UGI 013

Open-access endoscopy is important for early diagnosis of malignant lesions of the upper gastrointestinal tract

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Open-access endoscopy (OAE) is increasingly being viewed as an alternative to clinic referral for the diagnosis of upper GI pathology. Potential benefits include early diagnosis, in particular of malignant and premalignant lesions, and rapid institution of appropriate therapy and entry into controlled surveillance programmes when appropriate. This study prospectively evaluated our experience with OAE on 2000 consecutive referrals. All patients had proformas filled by their GPs giving patient details and complaints. These were reviewed by the surgeon and completed after endoscopy. Results, see table.

Diagnosis	Number (per cent)	Mean (SEM) age	Age vs benign	M:F
Carcinoma	85 (4·5)	66·6 (1·2)	$P < 0{\cdot}0001$	1·8:1
Oesophageal	23 (1·2)	68·7 (2·2)		1·9:1
Gastric	54 (2·8)	65·2 (1·5)		1·8:1
Barrett's	54 (2·8)	60·6 (2·0)	$P = 0{\cdot}0001$	1·8:1
CAG + int metapl	179 (9·4)	56·4 (0·9)		1·3:1
Benign	1401 (73·6)	53·2 (0·4)		1·3:1
Normal	362 (19)	48·6 (0·8)	$P < 0{\cdot}0001$	0·6:1

Statistics: Mann–Whitney U, Significance assumed at $P < 0{\cdot}05$ level.
CAG = Chronic atrophic gastritis plus intestinal metaplasia.

Endoscopy was performed on 1902 patients and had a diagnostic yield of 81 per cent. Carcinoma was diagnosed in 85 and included 54 gastric cancers of which 10 (18 per cent) were early, i.e. 1 in 190 endoscopies demonstrated early gastric cancer; 187 patients with potentially premalignant lesions were entered into surveillance programmes. In conclusion this study supports the wider introduction of OAE for the diagnosis of premalignant lesions and for the early diagnosis of malignant lesions of the upper gastrointestinal tract.

UGI 014

Vertical banded gastroplasty for morbid obesity

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The optimum surgical procedure for morbid obesity remains controversial. A personal series of 70 vertical banded gastroplasties (VBGs) performed over 15 years is presented.

Patients were selected by joint consultation between surgeon, medical gastroenterologist, psychiatrist and dietician. At operation a 25 ml reservoir was created with a 10 mm outflow tract constrained by a Gortex ring.

The median age of the patients at first presentation was 38 years (range 22–59 years), of whom 12 were male and 58 female. The median preoperative weight was 130 kg (range 91–200 kg) and the median body mass index (BMI) was 49 (range 33–77). Median follow-up was 2 years (range 6 months – 12 years) after which the median weight of the cohort was 103 kg (range 63–175 kg). The median BMI was 37 (range 23–55).

There were 2 deaths, 1 from pulmonary embolus and 1 from fulminant pancreatitis (mortality rate 2·9 per cent) and 7 major complications requiring either prolonged hospitalisation or revision surgery. Five patients described persistent postoperative vomiting.

The surgery for morbid obesity carries a high morbidity and mortality. Significant weight loss can be achieved by VBG in well-motivated, co-operative patients.

UGI 015

Gastric cancer: an evaluation of factors influencing survival

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Outcome in 734 patients presenting with gastric carcinoma in one centre over a 20-year period was reviewed. Forty-three per cent underwent resection, 12 per cent underwent gastroenterestomy or intubation and 45 per cent had no surgical treatment or no definitive surgery. Overall survival was 7 per cent, survival following curative resection was 28 per cent. Following curative resection, the presence or absence of serosal involvement ($P < 0.0005$), lymph node involvement ($P < 0.05$) and resection margin involvement ($P < 0.0005$) were found to be important predictors of survival.

Comparing the two periods 1974–1984 and 1985–1994, there was an apparent reduction in the proportion of patients undergoing 'curative' resection (39 per cent to 13·3 per cent; $P < 0.0005$) and a corresponding increase in the proportion of patients undergoing palliative resection (9·8 per cent to 24·1 per cent; $P < 0.0005$). There has been a reduction in the number of patients undergoing intubation (7·9 per cent to 1·2 per cent; $P < 0.0005$) and a corresponding increase in the proportion undergoing laser therapy. There has also been a reduction in the number of 'open and close' laparotomies (17·7 per cent to 7·6 per cent; $P < 0.0005$). Overall five-year survival decreased from 11 per cent in 1974–1984 to 6 per cent in 1985–1994 ($P = 0.013$). During the same period, five-year survival in patients undergoing curative resection improved from 24 per cent to 37 per cent ($P = 0.079$); this increase may reflect better staging rather than a genuine improvement in survival. These results suggest that outcome following surgery for gastric cancer has not improved over the last twenty years.

UGI 016

Does preoperative CT and operative assessment accurately predict the stage of gastric cancer?

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Accurate assessment of the tumour stage before and during laparotomy is important before decisions on appropriate surgery or neoadjuvant therapy are made for patients with gastric cancer. Presently computerised tomography (CT) scanning is the most widely used investigation for this purpose.

We have reviewed the CT findings, operative and final histopathological stage of 105 patients (M:F 73:32, median age 71 years) who underwent surgery for gastric cancer. The tumour was resected in 90 per cent of cases. The CT stage (TNM) and operative stage (TNM) were compared with the final histopathological stage.

Results:

	CT scan		Operative assessment	
Comparison with final histology	Final TNM	Node status (*n*)	Final TNM	Node status (*n*)
Correctly staged	58 per cent	54 per cent	75 per cent	69 per cent
Under-staged	35 per cent	41 per cent	10 per cent	11 per cent
Over-staged	7 per cent	5 per cent	15 per cent	20 per cent

Conclusions: Preoperative CT incorrectly staged 43 per cent of patients with gastric cancer and was even worse than operative assessment. These findings suggest that decisions about surgery and neoadjuvant therapy should not be based solely on the results of the preoperative CT scan.

UGI 017

Can radical lymphadenectomy be justified in the management of early gastric cancer?

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The technique of D2 lymphadenectomy achieves 5-year survival rates of >90 per cent for patients with early gastric cancer (EGC). Lymph node metastases are found in 10–15 per cent of cases, yet the role of radical surgery remains controversial. Our experience with EGC has been prospectively evaluated in order to determine the value of extended lymphadenectomy.

Over four years, 156 patients had surgical evaluation of gastric cancer and 28 (18 per cent) were found to have EGC. Twelve total and 14 subtotal gastrectomies were performed plus two completion gastrectomies for stump cancers. Fifteen patients had D1 lymphadenectomy performed because of a combination of age and coincident disease, the remainder had D2 gastrectomy. Histopathological evaluation was performed along UICC guidelines. Lymph node metastasis was found in 12 (43 per cent) cases. Metastasis was more likely in submucosal than mucosal EGC (9/14 vs 3/14; $P = 0.024$*). In two of the three cases with metastasis at the N2 level, the N1 nodes were entirely clear.

This study shows a higher incidence of lymph node metastasis than has been reported both in the UK and in Japan and may reflect meticulous histopathological techniques. Many patients were unfit for D2 lymphadenectomy and we have shown that clear N1 nodes do not guarantee an absence of metastases at the N2 level. The high incidence of lymph node metastasis in EGC supports the continuing use of radical lymphadenectomy for those patients who are fit for such major surgery.

*Fisher's exact test.

UGI 018

Results of surgical treatment with extended lymphadenectomy for oesophageal cancer

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The effects of three-field lymph node dissection (cervical, mediastinal and abdominal) were studied in 138 patients with squamous cancer of the thoracic oesophagus. Lymph node metastases were found in 91 (paragastric 38 per cent, paraoesophageal 36 per cent, recurrent laryngeal 29 per cent). There were 7 postoperative deaths (5·1 per cent). The 5-year cancer-specific survival was 42 per cent overall and 90 per cent, 34 per cent and 17 per cent in those with no lymph node metastasis, 1–3 involved nodes, and 4 or more involved nodes. Survival was more dependent on lymph node invasion than on adventitial invasion. Nodal metastasis occurred widely in the neck, mediastinum and abdomen even in those with 3 or fewer involved nodes, and could not be predicted by the site or depth of invasion of the primary lesion. Twenty-six patients had metastasis limited to one node group. The 5-year survival of 7 with involvement of the recurrent laryngeal group was 86 per cent in contrast to 25 per cent in the other 19. Of the 49 who died of recurrence, pure haematogenous spread was found in 37 (76 per cent) and lymphatic spread in 8 (16 per cent).

Lymph node metastasis can be assessed accurately by extended lymphadenectomy. Dissection along the recurrent laryngeal nerves appears essential for a satisfactory outcome. Following extended lymphadenectomy lymphatic recurrence is uncommon.

UGI 019

Prospective audit of the treatment of 100 consecutive cases of gastric cancer in a specialised surgical unit

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Both the Dutch and the MRC D1 vs D2 randomised studies have reported an increase in operative mortality (10–13 per cent) and morbidity (43–46 per cent) in patients who undergo the more radical Japanese style D2 resection compared with the less extensive D1 operation. However, this may be related to the experience of the surgeon and it has been suggested that better results could be obtained by concentrating such cases in specialised units.

We have carried out a prospective audit of 100 consecutive patients treated by one surgeon in a specialised unit over a three-year period (1993–95). Of these patients, 57 underwent radical and potentially curative D2 resection, 27 had a palliative resection, 4 palliative bypass and the remaining 12 patients had no surgical procedure. The median age of the patients was 70 years (range 33–92 years).

Operative mortality in the D2 resection group was 3·5 per cent (bronchopneumonia in 81-year-old and MI in 74-year-old) and morbidity was 9 per cent (small-bowel obstruction, haemorrhage, TIA and wound infection). There were no anastomotic leaks in this group and none of the deaths was directly attributable to surgical complications. In the palliative resection or bypass group ($n = 31$) operative mortality was higher at 9 per cent (bronchopneumonia in 2 patients aged 75 and 79 years and MI in a patient aged 78 years) and morbidity was 26 per cent.

Conclusions: These findings suggest that results of the surgical treatment of patients with gastric cancer in Britain could be improved if more of these patients were treated in specialised units.

UGI 020

Quality of life after radical (D2) resection for gastric cancer: results of a long-term follow-up study

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In Britain in the 1990s, an increasing proportion of patients with gastric cancer (GC) are being diagnosed at an earlier stage of disease, when cure by radical surgery is possible. Whilst the results of surgery have been based mainly on survival, very little information is available regarding the quality of life (QL) of those who survive such radical surgery.

We have assessed the physical performance (WHO score 0–4), social ability [Troidl index, Rotherdam Symptom Checklist (RSCL) part B] and psychological state [Hospital Anxiety and Depression (HAD) scale and RSCL part A] of 61 patients who underwent potentially curative (radical) (D2) resection for GC and compared these results to those of 32 age and sex matched controls who had not undergone gastrointestinal surgery.

Results:

	Proportion (per cent) who achieved satisfactory score		
QL assessment	Score	Patients (per cent)	Controls (per cent)
WHO scale	0–1	91	97
Troidl index	7–9	75	78
RSCL part B	17–24	83	91
RSCL part A	0–9	77	75
HAD scale	<16	95	91

Despite being underweight, most patients achieved a satisfactory score on these measurements of quality of life. There was no difference between those who had a total compared to those who had a subtotal gastrectomy. These findings suggest that, contrary to popular belief, most patients who survive radical surgery for GC enjoy a good quality of life.

UGI 021

An audit of gastric cancer surgery in Lothian – room for improvement?

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To audit surgery for gastric cancer in our region and identify potential for improvement, a case note review was performed of the 133 patients (80 male, 53 female, mean age 68 years, range 46–85 years) identified by the Lothian Surgical Audit who underwent surgery for gastric carcinoma in the 3 years up to December 1994. Preoperative staging included chest radiography in 115 (86 per cent), abdominal ultrasonography in 92 (69 per cent) and CT in 55 (41 per cent). Laparoscopy, performed in 31 (21 per cent) patients, was more common in 1994 than in preceding years (Chi square 15·3, $P < 0{\cdot}001$, 2df). Resection, performed by 18 different surgeons, included splenectomy in 36 patients with distal pancreatectomy in 19, with curative intent in only 47/133 (35 per cent). Serosal involvement (T3) was confirmed in 87 patients (65 per cent) and nodal metastases identified in 89 of the 128 specimens (70 per cent) assessed by the pathologist. Postoperative morbidity, predominantly cardiorespiratory, was recorded for 45 patients (34 per cent) and 8/31 (26 per cent) who underwent splenectomy. Thirty-day mortality was 12/133 (9 per cent). At a mean 13·2 months follow-up, 75/133 (56 per cent) patients were still alive.

This audit suggests that our patients present with late-stage disease, were inadequately staged preoperatively, suffer substantial postoperative morbidity and mortality (although splenectomy was not associated with increased morbidity) and have poor survival. Clearly there is room for improvement. Increased use of laparoscopy and laparoscopic ultrasonography for staging, preoperative systemic chemotherapy within clinical trials and the development of dedicated surgical units merit prospective audit.

H&P 011

Feeding the gut in acute pancreatitis: a randomised clinical trial of enteral vs parenteral nutrition

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Bacterial translocation is increasingly implicated as a potential initiator of the systemic inflammatory response syndrome (SIRS) and sepsis. In patients with major trauma, burns or critical illness, total enteral nutrition (TEN) significantly decreases the acute-phase response and incidence of septic complications compared to total parenteral nutrition (TPN). Poor outcome in acute pancreatitis is associated with a high incidence of SIRS and sepsis. Thus, TEN may have a therapeutic rationale in acute pancreatitis and the aim of this study was to examine this hypothesis.
Methods: Twenty-five patients with acute pancreatitis were evaluated for Glasgow, Apache II and CT scan scores, and C-reactive protein on admission. Patients were randomised to receive TPN or TEN for 7 days and then re-evaluated.
Results: The table shows results expressed as percentage change over seven days (*$P < 0{\cdot}05$ Wilcoxon signed rank).

	Glasgow	APACHE II	CT scan	CRP
TEN	–50 per cent	–33 per cent*	0 per cent	–49 per cent*
TPN	0 per cent	–10 per cent	0 per cent	+10 per cent

Hospital stay was significantly increased in the TPN compared to the TEN group [25 (15–38) vs 15 (12–29) $P < 0{\cdot}05$]. No TEN patient required ITU stay. Four patients in the TPN group required a median of 9·5 (5–12) days in ITU, one with a pancreatic abscess.
Conclusion: These data show that TEN improves disease severity, and reduces acute-phase response, despite unchanged pancreatic injury on CT scan. Thus mucosal feeding, perhaps via improved gut mucosal integrity, modulates the inflammatory and sepsis response in acute pancreatitis. This suggests the inflammatory drive in pancreatitis may result from both gland necrosis and translocation from the gut.

H&P 012

Laparoscopic ultrasonography in the staging of colorectal liver metastases: a prospective comparison with CT portography

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Laparoscopy with laparoscopic ultrasonography (LapUS) and CT portography (CTAP) are recent innovations which have been used in the preoperative staging of patients with colorectal liver metastases. A prospective comparison of both techniques was performed in 37 patients considered potentially suitable for hepatic resection with curative intent. Tumour unresectability was defined as extrahepatic, bilobar and/or vascular tumour invasion. The results were validated by (i) operative assessment of resectability, with palpation and intraoperative ultrasonography, and pathological examination of the resected specimen ($n = 25$), (ii) laparoscopic biopsy of extrahepatic tumour ($n = 4$), and (iii) the persistence or progression of a hepatic lesion on subsequent follow-up CT scans ($n = 8$). Resection for cure was performed in 20 patients, 'atypical' resection in 2 patients and non-therapeutic laparotomy in 3 patients.

Laparoscopy failed in one patient because of adhesions. The 'reference lesion', which was not visible laparoscopically in 13 cases (36 per cent), was imaged by LapUS in 35 cases. The diagnostic accuracies of CTAP and LapUS in predicting tumour unresectability are summarised in the table.

	CTAP	LapUS
Sensitivity	10/17 (59 per cent)	13/17 (76 per cent)
Specificity	14/20 (70 per cent)	19/19 (100 per cent)
Positive predictive value	10/16 (63 per cent)	13/13 (100 per cent)
Negative predictive value	14/21 (67 per cent)	19/23 (83 per cent)

CTAP should be interpreted with caution because of its poor specificity. LapUS is a sensitive and highly predictive method for determining tumour unresectability in patients with colorectcal liver metastases, and its use in a staging algorithm is recommended.

H&P 013

Cryosurgery for colo-rectal liver metastases

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Between October 1993 and October 1995 we have treated 45 patients with hepatic tumour using cryosurgery. This paper presents our early results and attempts to evaluate the role of this technique in the treatment of patients with irresectable colo-rectal liver metastases. Thirty-four patients (20 men and 14 women, with mean age 60, range 40–75 years) had colo-rectal liver metastases (range 1–14). There were 3 cases of carcinoid metastases, 1 renal cell carcinoma, 1 neuro-endocrine tumour and 1 small bowel schwannoma metastases. There were 2 cases of primary hepatomas. Seventeen patients underwent cryotherapy alone, 13 patients underwent combined cryotherapy and resection. Of the patients with metastases, the median number of lesions treated was 5. Mean operative blood-loss was 490 ml for cryotherapy treatment (range 100–2·25 litre). One patient died within 30 days due to ventricular arrhythmia (2 others in this series of 45 died within 30 days due to myocardial infarction, and 1 due to coagulopathy).

Six-month survival is 83 per cent (33 per cent disease-free) while the 12-month survival is 47 per cent (8 per cent disease-free). We conclude that cryotherapy is still in its early stages of evaluation, but as evident from our preliminary data, may offer survival benefit for patients with previously irresectable liver tumours.

H&P 014

Total pancreatectomy and simultaneous islet autotransplant for treatment of chronic pancreatitis

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Between September 1994 and August 1995, 6 patients (median age 48·5 years) underwent total pancreatectomy for chronic pancreatitis. The spleen was preserved in 4 patients. Immediately after resection, the pancreas was transferred to the laboratory where the islets of Langerhans were isolated using a combination of collagenase digestion and density gradient purification. The islets were then transported back to theatre. In all 6 patients, islets were embolised into the liver via the portal vein (median transplanted volume = 8·5 ml) and in addition 3 patients had islets embolised into the splenic sinusoids via short gastric vein (median transplanted volume = 4 ml). Postoperatively, endogenous insulin production was monitored by serum C-peptide levels.

One patient died of a stroke 4 weeks postoperatively. Of the 5 surviving patients, all have C-peptides in the normal range (median = 2·94 ng/ml). Four patients are now insulin-independent and the remaining patient requires only 4 units once daily. All 5 patients are pain-free.

We conclude that when total pancreatectomy is performed for the treatment of chronic pancreatitis, it should be combined with an islet autotransplant. By combining the intraportal and intrasplenic routes of transplantation, it is possible to minimise the risk of portal hypertension.

H&P 015

Radical resection of hepatic tumour by a new technique of transverse hepatectomy with *ex vivo* liver dissection

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A 56-year-old woman presented with a right colon cancer in December 1994 and underwent right hemicolectomy. Preoperative liver ultrasound had suggested liver metastases and this was confirmed at laparotomy. She made a good recovery and was referred for consideration of hepatic resection.

Liver MRI demonstrated a caudate lobe (segment 1) metastasis compressing the inferior vena cava (IVC) and invading anteriorly through hepatic segments 2 and 4A (left liver). A second metastasis was isolated in segment 8 (right liver) invading segment 7 and affecting the right and middle hepatic veins at the inferior vena cava.

Laparotomy with intra-operative ultrasound confirmed the radiological findings. The portal triad and IVC were divided and the liver removed to the bench, flushed with preservation solution and the patient was placed on veno-venous bypass. Four hours of bench dissection resulted in reimplantation of segments 4B, 5 and 6 with anastomosis of intrahepatic stumps of the right and middle hepatic veins to a 22-mm Dacron graft to replace the IVC.

At 8 months the patient remains tumour free. Although an early progress report, this case demonstrates that modern hepatic surgery is challenging 'inoperable' tumours.

H&P 016

Results of split liver transplantation

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Split liver transplantation offers a way of increasing the number of donor grafts available at a time when the overall number of cadaveric donors is decreasing. Early results reported were disappointing due to patient selection and technical complications. We report our early experience of splitting 8 cadaveric donor livers.

Livers from 8 cadaveric donors (mean age 23 years, range 10–47; mean weight 67 kg, range 30–95) were split. Of the 16 grafts, 14 were transplanted in our centre (8 left lateral segments and 6 right lobes) and 2 grafts were exported. Eight left lateral segment recipients (mean age 7·5 years; mean weight 20 kg, range 8–31) were transplanted. Mean cold ischaemic time was 10·5 hours (range 6·5–15). Postoperative complications included ascites in one and recurrent cholangitis due to kinked Roux loop in one which was retransplanted for secondary sclerosing cholangitis. Two children died, one following an intracranial bleed 8 days post-transplant and the other from venous outflow obstruction.

Six right lobe recipients (mean age 36 years; mean weight 53 kg, range 32–63) were transplanted for chronic liver disease. Mean cold ischaemic time was 15·8 hours (range 12·5–19). Postoperative complications included segment IV necrosis in one patient.

Median follow-up is 10 months (range 1–52). Graft and patient survival is 85·7 per cent.

Split liver transplantation represents an innovative way of increasing the number of donor grafts available and should be used in stable/good-risk recipients.

Vascular 020

Fatal pulmonary embolism: still missing the boat

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Mechanical and pharmacological methods are effective in reducing the incidence of thromboembolic disease and risk factors are established, yet patients continue to die from pulmonary embolism (PE). Deaths amongst surgical inpatients in Scotland due to fatal PE were studied to determine the level of risk and prophylaxis used. Each patient was allocated to a risk group using the THRIFT[1] criteria. Cases were identified from the Scottish Audit of Surgical Mortality.

During 1994, 57 deaths due to PE were identified, 39 in a high-, 17 in a moderate- and 2 in a low-risk group. Only 25 (44 per cent) had received any form of prophylaxis: 22 patients (56 per cent) in the high-risk group, 3 patients (16 per cent, $P = 0·003^*$) in the moderate-risk group. Thirty-nine (68 per cent) were emergency admissions; of these 11 patients (28 per cent) received prophylaxis. In contrast, 14 of the 18 elective admissions (78 per cent) received prophylaxis ($P = 0·008^*$).

Three groups of patients were clearly identified as being less likely to receive prophylaxis: those in a moderate-risk group, emergency admissions and those managed conservatively. If the mortality and morbidity of thromboembolic disease are to be reduced, all patients should be assessed for risk factors and appropriate prophylaxis prescribed from the time of admission.

[1] Risk of and prophylaxis for venous thromboembolism in hospital patients. Thromboembolic Risk Factors (THRIFT) Consensus Group. Br Med J 1992; 305:567–574.

*Chi-squared test with Yates correction.

Vascular 021

Complications of IV drug abusers: 4-year prospective study

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The prevalence of vascular complications in parentral drug addicts in Britain is sparse in the literature. Over a 54-month period, a prospective study was undertaken to identify the spectrum of vascular problems in drug addicts at our hospital. All patients were tested for HIV, hepatitis B and hepatitis C (since availability) status. Patients were assessed by colour flow Doppler ultrasound analysis.

During the study 29 vascular complications occurred in 14 patients, mean age: 32·5 years, male:female ratio: 6:1. Eight of fourteen (57 per cent) patients had multiple admissions. Complications noted were 5 femoral false aneurysms (4 leaking) and 1 popliteal false aneurysm (leaking), 6 distal arterial embolisations, 7 femoral deep-vein thrombosis and 10 groin abscess close to an uninvolved major blood vessel. All patients were HIV –ve, with 3 hepatitis B +ve and 6 of 9 (66 per cent) positive for hepatitis C. Four femoral false aneurysms were treated by ligation of the artery with no limb loss. One required an extra-anatomic bypass which got infected due to further needling. Distal arterial embolisations resulted in either skin or digit loss in all cases. Abscesses were treated by either open drainage or tube drainage under ultrasound guidance. One limb was amputated. No mortality occurred.

This study highlights the spectrum of vascular complications in intravenous drug addicts. Femoral artery ligation without bypass (which can be needled) is often safe. Colour flow Doppler ultrasound assessment is recommended as it is less hazardous than angiography to the radiologist. Hepatitis C (for which currently no vaccination is available) status should be checked in all cases. Proper counselling may be required to reduce readmissions.

Vascular 022

Management of acute leg ischaemia in the elderly

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Acute arterial ischaemia is a major cause of morbidity and mortality, particularly among the elderly. Intra-arterial thrombolysis and catheter embolectomy are the most common treatments, but there is increasing evidence to suggest that thrombolysis carries a high risk in elderly patients. A retrospective comparison was made of the outcome of primary surgical intervention vs primary thrombolysis in 77 patients over the age of 75 years, presenting to one vascular unit.

Thirty-seven patients were treated primarily with intra-arterial thrombolysis. Their median age was 82 (range 75–92) years, and they presented with a median duration of ischaemia of 60 hours (range 3 hours to 14 days). Sixty-five per cent had rest pain. Thrombolysis was performed on 26 native vessel occlusions and 11 bypass grafts, tissue plasminogen activator was used in 31 cases and streptokinase in 6 cases. The 30-day outcome for the thrombolysis group was 51 per cent limb salvage, 3 per cent amputation and 46 per cent died.

Twenty-nine patients were treated with primary surgery (25 embolectomies, 3 bypass grafts and 1 primary amputation). Their median age was 83 (range 75–98) years, the median duration of ischaemia was 24 hours (range 3 hours to 14 days). Ninety-six per cent had rest pain. All occlusions were in native vessels. The outcome of the surgical group was 69 per cent limb salvage ($P = 0·07$, compared to lysis: Fisher's exact test), 3 per cent amputation and 28 per cent died.

In the same time interval 11 patients were treated conservatively with anti-coagulation and analgesia. Their median age was 82 (range 75–100) years and the median duration of ischaemia was 24 hours (range 2 hours to 7 days). Seventy-eight per cent had rest pain. All occlusions were in native vessels. At 30 days 82 per cent had died and 18 per cent survived with intact limbs ($P = 0·02$ compared to surgery and $P = 0·09$ compared to thrombolysis: Fisher's exact).

These results suggest that, for the elderly presenting with acute limb ischaemia, in appropriate cases, a quick thrombo-embolectomy, under local anasaethesia, may be preferable to thrombolysis.

Vascular 023

A cost analysis of limb salvage in diabetic critical limb ischaemia

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Aim: The objective of this study was to analyse the overall cost of diabetic limb salvage for critical limb ischaemia (CLI) one year following revascularisation.

Patients and methods: Sixty lower limbs with CLI in 47 diabetic patients were recruited prospectively between June 1993 and June 1995. CLI was defined as ischaemia that endangers the whole or part of a limb. Treatment costs, except transport and home care, were assessed for the 12 months following intervention. Patients were stratified into those undergoing percutaneous transluminal angioplasty (PTA – group 1) alone and those in whom surgical revascularization, with or without adjuvant PTA, was felt to be the most appropriate primary treatment (group 2). For the purposes of the study limb salvage was defined as the presence of a viable foot for walking.

Results: Patients included 29 women and 31 men (median ages: group 1 – 73·0 years, group 2 – 76·5 years). No significant difference was demonstrated in age, sex ratio, percentage of insulin-dependent diabetics and risk factors between groups 1 and 2. Overall mortality was 17 per cent and there was no significant difference between the two groups. The median costs at 12 months' follow-up were significantly (MW; $Z = 5·54$;

$P < 0{\cdot}001$) less for group 1 (£2099, range £1046–£11 710) than for group 2 (£7227, range £3756–£54 558). This was thought to be due to the length of in-patient stay but this was not significantly different between the two groups. However, analysis of the patients requiring secondary intervention or adjuvant PTA confirmed that this group accounted for the difference. Limb salvage was attempted in all patients and was successful in 83 per cent.

Conclusions: The cost of uncomplicated revascularisation by either PTA or surgery appears not to differ significantly in the diabetic population. However, failed primary revascularisation can result in significantly greater expense and prolonged in-patient stays (MW = Mann–Whitney Test).

Vascular 024

The role of iliac stenting in the management of critical limb ischaemia

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Endovascular surgery has an increasing role in the management of critical limb ischaemia.

The results of 19 consecutive iliac stents in 15 patients with critical limb ischaemia are reported. The mean age was 63 years (range 45–77) and the male:female ratio 12:4. All procedures were performed in the operating theatre using C-arm image intensification. Concomitant radial and femoral arterial pressures were measured at surgery. The mean pre-stent pressure difference was 30 mm Hg (range 0–70) and this increased to 50 mm Hg (range 15–80) following intra-arterial papaverine. Palmaz stents were used in all cases after exposure and control of the femoral vessels. Eleven concomitant vascular procedures were performed: six femoro-femoral bypasses and five femoro-popliteal bypasses.

The mean follow-up is 15 months (range 4–50). There was one primary failure requiring an aorto-femoral bypass. One artery restenosed at the stent site at 36 months with failure of the femoro-femoral bypass and was restented. All the remaining stents are patent with no evidence of recurrent stenosis and all concomitant bypasses are patent.

These results indicate that iliac artery stenting is a useful adjunct in the management of critical limb ischaemia and should be part of the armamentarium of the vascular surgeon, particularly as a concomitant vascular procedure is frequently required.

Vascular 025

The treatment of total iliac occlusions with the Memotherm self-expanding Nitnol stent

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Twenty-six patients with total iliac occlusions were submitted for recanalisation angioplasty with stenting over a 16-month period. Initial recanalisation was successful in 23 patients (88 per cent) and was followed by intravascular stenting. The Memotherm self-expanding Nitnol stent was utilised in 20 patients. All procedures were carried out by one radiologist and followed up for a minimum of 3 months.

The 23 successful recanalisations occurred in 14 men and 9 women with an age range of 44–86 years. Seven legs had critical ischaemia and 16 intermittent claudication. Mean ankle pressure was 74 mmHg (range 0–114). Occlusion locations were: 16 common iliac, 3 external iliac and one involving both vessels. The average occlusion length was 60 mm (range 20–110). Bilateral aortic bifurcation stenting was performed in 10 patients; in 6 due to contralateral common iliac disease and in 4 to provide contralateral support.

Satisfactory stent deployment was achieved in all cases. A single stent sufficed for each occlusion in all but one patient. Complications were a thrombosis in the external iliac artery distal to a common iliac stent and four groin haematomas, none requiring surgical intervention. Mean fluoroscopy time for the procedure was 11·7 minutes (range 3·2–25·4).

Twenty-two patients showed immediate clinical improvement. Mean ankle index improved from 0·47 to 0·82 mmHg at three months (paired $t = 6{\cdot}99$; $P < 0{\cdot}001$). There have been no reocclusions in the 22 patients treated without complication. The Memotherm stent has proved highly successful in the treatment of total iliac occlusions, offering significant technical and financial advantages and represents a major advance in intravascular stent design.

Vascular 026

Cost effectiveness of percutaneous transluminal angioplasty

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Introduction and aims: Percutaneous transluminal angioplasty (PTA) is a commonly used intervention for claudicants; however little has been reported regarding its cost effectiveness and its impact on patients' quality of life (QOL). This study aimed to assess the cost effectiveness of PTA and its impact on clinical indicators of lower limb ischaemia and patients' QOL using the EuroQol(EQ) questionnaire.

Patients and methods: Thirty claudicants (12 women and 18 men), median age 66 years (range 42–82 years), underwent 37 PTAs, 19 supra- and 18 infra-inguinal, with approximately equal numbers of stenoses and occlusions in each group. Ankle brachial pressure indices (ABPI) and maximum treadmill walking distance (MTWD) were measured before completing the EQ questionnaires at interview, 1 day prior to, and 1 and 3 months after PTA.

Results: Statistical analysis using Kruskal-Wallis Anova showed a significant improvement in ABPI, MTWD and EQ measures of dimensions of mobility, pain, usual activities and anxiety/depression ($P = <0{\cdot}01$). Using the data from the EQ visual analogue scales, PTA results in a gain of 2·8 quality-adjusted life years (QALYs) and this equates to a cost of £438·50 per QALY.

Conclusion: PTA improves clinical indicators of lower limb ischaemia and EQ measured domains of QOL. Interestingly, however, at 3 months there was a downward trend in several QOL domains which did not reach statistical significance. This deserves further study. PTA would appear a cost effective choice in the treatment of claudicants, in the short-term at least.

Vascular 027

Management of acute limb ischaemia – at what cost?

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Recent American trials have shown that a minimally invasive approach to the management of acute lower limb ischaemia (ALLI) is more effective than open surgery. There is, however, little information on the cost of these procedures. The costs of attempting limb salvage in patients presenting with acute limb ischaemia to one district general hospital were prospectively recorded for 18 months.

Seventy-five patients were admitted with ALLI during the study, 45 were treated radiologically and 18 had primary surgery. The remainder were treated conservatively. Patients receiving primary surgery were older and had more severe ischaemia than the radiological group, all but one of whom received intra-arterial thrombolysis. Other clinical factors were similar. Limb salvage at 30 days was 39 per cent in the surgical group, and 80 per cent for the radiology group, consistent with the hospital's policy for managing ALLI. The costs for the initial procedure (disposable equipment, non-medical staff costs and the cost for occupation of the X-ray suite or theatre), secondary intervention, complications and inpatient bed costs were calculated for both groups and expressed as median values.

The surgical group required significantly fewer vists to theatre (1, range 1–3) compared with the radiological group (3, range 2–4, $P < 0{\cdot}0001$, Mann–Whitney) but there was no difference in the total time that theatre or the radiology suite was occupied [2·3 hours (1·5–5) and 3 hours (2–5) respectively, $P = 0{\cdot}1$]. The cost of disposables for performing surgery was significantly lower than those for thrombolysis [£82·00 (58–169) and £407 (252–596) respectively, $P < 0{\cdot}0001$]. When the cost for using the theatre or radiology suite was included, the costs of both treatments were similar [surgery: £683 (309–1438) vs lysis: £861 (611–1244)]. The median inpatient stay for surgery was not significantly different to that for thrombolysis [9 days (3–18) and 11 days (2–29) respectively]. Costs for bed occupancy were similar in both groups [£2497 for surgery (643–9115) and £2189 (902–6020) for lysis, $P = 0{\cdot}5$]. Total cost for attempting limb salvage by surgery was £3429 (1094–10065) compared with £3230 (1543–8353, $P = 0{\cdot}8$) for thrombolysis.

This study showed that the costs of primary intervention using surgery or thrombolysis for acute limb ischaemia are similar, and that the final cost depends on the severity of underlying disease and therefore whether further treatment is necessary.

Vascular 028

Anastomotic vein cuffs protect run-off vessels in femoro-distal polytetrafluoroethylene bypass

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The use of a distal anastomotic vein cuff improves patency in infrageniculate prosthetic grafts, probably in part by its effect on anastomotic myointimal hyperplasia. This prospective study examines the effects of graft occlusion in the presence of a vein cuff.

In a series of 87 consecutive infra-inguineal polytetrafluoroethylene (PTFE) grafts with adjuvant distal anastomotic vein cuff, performed for critical limb ischaemia, the cumulative patency rates were 78 per cent, 68·5 per cent and 60·5 per cent at 6, 12 and 18 months respectively. Of 37 grafts which occluded, 22 were investigated by angiography (no angiography was performed in 15 grafts, due to immediate re-exploration for early failure). The run-off vessel was preserved in 19 (86·4 per cent) and occluded in 3. The vein cuff was fully or partially patent in 8 (36·4 per cent) and occluded in 14. Revascularisation of the original recipient artery was possible in 13 and the same cuff was reused in 2 cases. Examination of explanted anastomoses showed accumulation of myointimal hyperplasia within the vein cuff but very little in the recipient artery.

Prosthetic graft failure is usually associated with occlusion of the recipient artery and a variable amount of the run-off circulation. This study suggests that when PTFE grafts fail in the presence of a vein cuff, patency of the recipient artery and run-off circulation is usually preserved due to changes in the distribution of myointimal hyperplasia. This may enhance the prospects of a further successful revascularisation procedure.

Vascular 029

Arm-calf pulse volume recording transfer function versus ankle: branchial pressure index in peripheral vascular disease

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Ankle:brachial pressure index (ABPI) is the first investigation of peripheral arterial disease. Its results are variable; it affords no separation of supra- and infra-inguinal disease.

Pulse volume recording transfer function (PVRTF) is a screening test being developed for peripheral vascular disease (PVD). Pulse volume waveforms are collected from an arm cuff (PVL 50, Scimed, UK) and a frequency response curve (the input) is derived. A further frequency response curve (the output) is generated from a calf cuff. Division of the input and output frequency response curves produces a transfer index.

One hundred and twenty-six legs in 63 patients with PVD were assessed with ABPI and arm-calf PVRTF; the tests were broadly comparable (correlation coefficient = 0·68).

As arm-thigh PVRTF indicates aorto-iliac disease, the addition of arm-calf PVRTF allows the prospect of a simple screening test that will be able to reflect the relevant contributions of supra- and infra-inguinal segments.

Vascular 030

A rational approach to leg ulcer treatment: the use of colour duplex scanning in community leg-ulcer patients

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Superficial and/or deep venous dysfunction frequently underlie chronic ulceration of the lower limb. As an attempt to rationalise treatment, we have used colour duplex ultrasonography as a primary investigation in patients attending community leg-ulcer clinics.

All patients with chronic leg ulceration who had an ankle:brachial pressure index ≥ 0·85 underwent duplex scan assessment of the superficial and deep venous systems of both legs.

One hundred patients (66 female : 34 male) with 111 ulcerated limbs were examined. Mean age was 69 years (range 29–88). Mean duration of the ulcer was 11 months. Previous venous surgery had been undertaken in 41 (39 per cent) ulcerated legs and 28 (34 per cent) contralateral legs. Fifty-one per cent of ulcerated limbs had isolated superficial venous dysfunction in the absence of deep disease.

Duplex scanning provided early diagnosis of the venous pathology in patients attending our community leg-ulcer clinics. This identified patients suitable for surgical correction of isolated superficial disease.

Results:

	Incompetence pattern			Deep occlusion	Normal study
	Superficial	Deep	Mixed		
Ulcerated ($n = 111$)	57 (51%)	6 (5%)	42 (38%)	2 (2%)	4 (4%)

Vascular 031

Stable vortices within vein cuffs inhibit anastomotic MIH?

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Interposition vein cuffs improve the patency of below knee polytetrafluoroethylene arterial grafts and there is evidence to show that they do so, at least in part, by modifying the distribution of myointimal hyperplasia (MIH) at the distal anastomosis. Alteration of local haemodynamics is one of the mechanisms which might be involved. Flow patterns have been analysed in a laboratory model of cuffed and uncuffed anastomoses and compared with observations made in patients by cine intra-arterial digital subtraction angiography and dynamic colour Duplex scanning.

Laboratory experiments in the anastomotic model showed that flow in a cuffed anastomosis is associated with the formation of a stable vortex. This is in contrast to non-cuffed anastomoses in which flow is predominantly laminar. Rotational flow within the vortex is unidirectional and therefore exerts potentially higher mean shear stress on the arterial wall than normal bidirectional laminar flow. The clinical studies confirmed that vortices with identical characteristics are a constant feature of cuffed anastomoses in patients.

Since MIH is thought to be promoted by contact between blood constituents and the arterial wall, and inhibited by high shear stresses, it may be that the optimal configuration of anastomoses is that which most effectively promotes the formation of this type of vortex.

G/U 001

Day-case laparoscopic hernia repair

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Laparoscopic hernia repair within the UK began at the Royal Shrewsbury Hospital in June 1992, since when more than 700 TAPP hernia repairs have been done. In June 1994, the Day-Surgery Unit opened and all patients medically and socially suitable have since been treated by the consultant as day-cases.

Up to 7 hernias have been repaired in a session in never more than five patients. One hundred and fourteen patients have undergone surgery and 112 have been discharged the same day. The procedure was unilateral in 93 patients and in 21 bilateral. Eleven patients were operated on for recurrent hernia (10 following open operation) and there were 11 sliding hernias. In more than 10 per cent of patients with apparent one-sided pathology, there was a contralateral hernia on laparoscopy.

Following discharge, 1 patient required readmission and to date there has been 1 recurrence. More than 35 per cent of patients treated as a day-case took no analgesia after leaving hospital. All patients were reviewed at two weeks and subsequently contacted by mail or phone. Complications have been minimal and transient. The operation appears cost effective and has proved advantageous, particularly for patients with bilateral and/or recurrent hernias and to all those wishing to return rapidly to work and sporting activities. As nearly all patients under the age of 70 are suitable for day-case surgery, this lowers the demand for in-patient beds and theatre times and helps to meet the demands of the Patient's Charter.

G/U 002

A study of postoperative pain in patients undergoing repair of inguinal hernia by the Lichtenstein and Shouldice techniques

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Fifty consecutive patients with unilateral non-recurrent inguinal hernias were randomised to undergo repair using the polypropylene mesh or Shouldice technique by a single surgeon using either local or general anaesthesia. Anaesthetic techniques were standardised.

Postoperatively all patients received a supply of oral analgesia comprising morphine sulphate and dicofenac sodium. Postoperative pain was assessed on a linear analogue scale at 1 and 24 hours and 4 weeks postoperatively. At 1 hour there was a significantly lower pain score in patients who had undergone either procedure by local anaesthetic compared with general anaesthetic (0·9 vs 5·5 $P < 0{\cdot}01$). The difference was not maintained at 24 hours (2·8 vs 4·8). There was no significant difference in the pain scores between Shouldice and Lichtenstein repairs at 1 (2·0 vs 2·4) and 24 hours (1·9 vs 4·6). At 4 weeks there were no significant differences in pain scores for any of the patient groups. There was no difference in the quantity of postoperative analgesia taken by patients analysed by repair type or anaesthetic type.

These results do not support the hypothesis that mesh repair is less painful than Shouldice repair.

G/U 003

Exclusion from day-case surgery: a one-year clinical audit

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The implementation of day-surgery increases the efficiency of provision of surgical services. Day-unit based audit does not detect patients admitted for inpatient surgery who would be suitable for day-surgery. We undertook a one-year prospective study of patients added to our waiting list for inguinal hernia (IH) repair or ligation and stripping of varicose veins (VV).

The reasons for exclusion from day-surgery were recorded in patients with IH or VVs for whom inpatient surgery was planned. Analysis of the results included review of indications for admission by the consultants responsible for the day-unit, who assessed whether the patient would have been suitable for day-surgery.

Two hundred and seventy-seven patients were booked for IH surgery, 160 (58 per cent) as day-cases, and 346 patients for VV surgery, 271 (78 per cent) as day-cases. Fourteen IH and 32 VV patients were incorrectly booked for admission. We identified some of the reasons behind this. Had these been booked, appropriately 63 per cent of IH and 88 per cent of VV surgery would have been planned as day-surgery.

In a unit exceeding the most optimistic Audit Commission targets, clinical audit has revealed room for improvement, which can be implemented with a few simple measures that we outline.

G/U 004

Abdominal wound skin closure using a new tissue adhesive formulation

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The development of a new formulation has allowed a transparent *n*-butyl 2-cyanoacrylate-based glue for closure of abdominal skin wounds. Utilising this glue for skin closure offers the potential advantages of combining an accurate, reliable and suture-free method of skin approximation with a transparent sterile bacteriostatic biodegradable occlusive dressing. We analysed this new tissue adhesive for abdominal wound skin closure.

Patients undergoing abdominal surgery were enrolled into this study. Following haemostasis of the skin wound, the edges were approximated, the adhesive glue, *n*-butyl 2-cyanoacrylate, was applied along the edge of the wound and maintained in position for ten seconds. Postoperatively, the wounds were inspected for any complications.

Wound size (cm)	*n*	Complications
1–3	154	0
5–8	25	0
10–35	37	3

The complications seen included two instances of small superficial skin dehiscence and one small serous collection. No further operative intervention was required in any of these cases. There were no wound infections.

The results of this study indicate that the adhesive glue can be used as a reliable and safe method of wound closure. It may well confer a significant advantage over the more traditional methods of skin closure.

G/U 005

A traumatic deterioration in general surgeons' access to emergency theatre

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Aim: To assess delays in emergency theatre provision for general surgical cases.
Setting: Two previous audits have been undertaken, before and after provision for a 24-hour emergency theatre[1]. These demonstrated a reduction in late-night operations and waiting time. A third audit was undertaken following the appointment of 2 new trauma consultants, to assess their effect on access by general surgeons to emergency theatre.
Methods: Prospective audit of 2 months' emergency work (May, June, for all 3 audits in successive years).
Results: Table illustrating number of emergency cases and timing of emergency surgery.

Time	1st audit	2nd audit	3rd audit	
0900–1700	40 (29·4%)	71 (61·3%)	52 (39%)	1&2 $P < 0{\cdot}001$ 2&3 $P < 0{\cdot}001$
1701–2400	67 (49·3%)	38 (32·4%)	55 (41·3%)	1&2 P 0·005
0001–0859	29 (21·3%)	7 (6·3%)	26 (20·7%)	1&2 $P < 0{\cdot}001$ 2&3 $P < 0{\cdot}005$

During the third audit 71 emergency operations were scheduled for 0900–1700; only 67 per cent were undertaken during this time. The general surgical scheduled 'emergency slot' was 1100–1300, 22 patients were operated on in these hours. Nine suffered no delay, 13 were delayed for up to an hour, and 5 for greater than 1 hour. Thirty-two of the 44 trauma lists scheduled for 0900–1100 over-ran.
Conclusion: The appointment of 2 new trauma surgeons has materially contributed to a significant deterioration in provisions for general surgical emergencies. Large district general hospitals need separate facilities for trauma and general emergencies.

[1] Theatre delay for general surgical emergencies: a prospective audit. College and Faculty Bulletin. Ann. R. Coll. Surg. Engl. 1995; 77: 121–4.

G/U 006

Port site metastases in patients undergoing laparoscopy for gastrointestinal malignancy

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Laparoscopic colonic resections and laparoscopy for the assessment of malignant disease have been advocated. Isolated reports describe metastatic deposits at port sites. The purpose of this study was to determine the early incidence of port site metastases and attempt to define factors that might influence their occurrence.

Thirty-nine patients (median age 65, range 21–90) with gastrointestinal malignancy underwent laparoscopy. Five patients had laparoscopically-assisted colonic resections. Another had a laparoscopy for bowel obstruction immediately prior to laparotomy for an obstructing caecal carcinoma. The remainder underwent laparoscopy for staging of gastric (7 patients) or oesophageal carcinoma (26 patients). Assessment was made of the presence of liver metastases, ascites, omental or peritoneal deposits and lymph node involvement. Twenty patients had their tumours resected. Patients were followed up until death.

Twelve patients died a median of 3 (range 1–12) months after laparoscopy, 4 following colonic resection, 8 with gastro-oesophageal malignancy (four resections). Median (range) follow-up of the 27 survivors is 9 (1–36) months. Four of 16 patients with tumour involving serosal surfaces developed port site recurrences compared with none of 23 without serosal involvement ($P < 0{\cdot}05$). Two patients with gastric carcinoma developed umbilical port site recurrence, 1 month and 7 months respectively after laparoscopy. Both died within two months of developing port site recurrence. The third patient, who had a hemicolectomy for a Dukes' B caecal carcinoma following diagnostic laparoscopy, developed a port site recurrence 15 months after surgery. The fourth patient had a laparoscopically-assisted sigmoid colectomy for an advanced obstructing sigmoid tumour and developed a port site recurrence 6 months postoperatively. This early incidence of port site recurrence in this cohort of patients was 10 per cent. Incidence in the long-term is likely to be higher. Port site recurrence may be related to serosal involvement with tumour.

G/U 007

What does a weekend 'on-call' in a surgical oncology ward do to cognitive performance and mood?

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As considerable interest and concern have been expressed about junior doctors' hours, a study was carried out to evaluate the emotional and cognitive effects of a weekend 'on-call' in a surgical oncology ward.

Ten surgical house officers were assessed, in counterbalanced design, on four Monday mornings, twice after a weekend off-duty and twice after a weekend 'on-call'. Cognitive functioning was assessed using the CDR Computerised Cognitive Assessment System and emotional state was evaluated by means of the Mood Rating Scale (150 mm visual analogue scales). When 'on-call', doctors worked on average from 07·20 hours on Saturday to 01·09 hours on Sunday and from 07·40 hours on Sunday to 00·55 hours on Monday (just over 35 hours in total). They were bleeped on average 3·1 times on Saturday and 2·1 times on Sunday nights and they visited the wards on average 1·4 times on both nights. When on-call, they slept an average of 4 hours 30 minutes on Saturday night and 4 hours 9 minutes on Sunday night in contrast to 8 hours 6 minutes and 6 hours 27 minutes on weekends off-duty.

A weekend 'on-call' had several significant adverse cognitive and emotional effects:

Measure	Off-duty mean (SE)	On-duty mean (SE)	P
Attention (speed) (msecs)	1153 (33)	1211 (36)	0·05
Vigilance sensitivity index	0·96 (0·01)	0·92 (0·02)	0·025
Energy	74 (9)	25 (7)	0·001
Clear headedness	99 (10)	69 (9)	0·007
Confidence	93 (8)	81 (8)	0·04

Impaired attention, working memory and long-term memory, and confusion, were most closely correlated with number of hours worked on Sunday, whereas tiredness and confusion were related to number of hours slept.

The emotional and cognitive effects of a weekend 'on-call' have implications for the optimal design of duty rosters.

G/U 008

Can psychomotor testing be used to predict outcome following major surgery

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Risk-factor analysis for outcome following surgery has concentrated on physiological scoring systems which require accumulation of data which precludes immediate prognostication. This study examines the clinical usefulness of a simple functional assessment of elderly patients undergoing major surgery. Disability was scored by examining lower extremity function (LEF) by standing balance, walking speed and ability to rise from a chair. Patients were also scored for maximum arm reach and time taken to perform their signature. Thirty-one patients underwent major thoracic, vascular or general surgical procedures and were graded into four groups depending on outcome: uneventful postoperative course (none, n = 11), minor complications (minor, n = 10), major complications (major, n = 7) and died (died, n = 3). Results: see table, expressed as mean (SEM). High scores indicate a good performance.

Group	Number	LEF score*	Signature**
None	11	4·6 (0·2)	0·94 (0·32)
Minor	10	4·0 (0·2)	0·85 (0·05)
Major	7	3·5 (0·2)	0·5 (0·09)
Died	3	3·8 (0·3)	0·65 (0·07)

Statistics used ANOVA * $P < 0·03$; ** $P < 0·005$.

Progressive deterioration in outcome occurred with lower preoperative scores for both LEF and signature speed. LEF scores inversely correlated with both intensive-care unit stay (days) ($r^2 = 0·298$; $P < 0·02$) and postoperative hospital stay (days) ($r^2 = 0·065$; $P < 0·002$). These preliminary results indicate that this scoring system which relies on assessment of both upper and lower limb function may provide a simple method of predicting outcome in patients undergoing major surgery.

G/U 009

Simultaneous pancreas and kidney transplantation: early results from a new centre

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This is the first report of results from our centre since beginning pancreas transplantation in September 1992. We have carried out 14 simultaneous whole-organ pancreas and kidney transplants. Donor organs were retrieved with preservation of the coeliac axis for the liver which was transplanted in each case, and the use of donor iliac artery Y-graft reconstruction of the pancreatic blood supply. Organ implantation was done through a short lower midline abdominal incision, placing the kidney extraperitoneal and the pancreas intraperitoneal with duodenocystostomy in the first 12 patients. Urine amylase and pH measurements were not helpful and enteric conversion was needed in 4. Therefore, primary enteric anastomosis of the donor duodenum has been done in the last 2.

The patient population offered for the new programme has been high risk: 3 have died on the waiting list. Two patients died post-transplant from cardiovascular diabetic complications and one from cytomegalovirus infection. One pancreas has thrombosed. Currently 11 patients have good kidney function and 10 have normal blood glucose control, evidenced by fasting and post-prandial blood sugar series, oral glucose tolerance tests and HbA1c.

Pancreas transplantation has been slow to develop in the UK. Acceptable results are now being achieved in seriously ill recipients. Wider application of the procedure should now be encouraged.

G/U 010

Ten-year review of splenic injury – is there an increasing place for conservative management?

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Splenic conservation is important in order to avoid overwhelming post-splenectomy infection (1–2 per cent in adults, higher in children, with up to 50 per cent mortality). Deaths occur despite splenic auto-transplantation. It has been suggested that over 30 per cent of splenic injuries should be managed conservatively. Splenic injuries for a 10-year period have been retrospectively analysed.

Results:

Number	1985–1990	1990–1995
Total	47	62
Splenectomy	40	35
Splenorrhaphy	3	6
Non-operative	4 (1 failure)	21 (2 failures)
Conserved	6 (13 per cent)	25 (40 per cent)

*$P < 0·05$ Fishers Exact.

Although there is no defined protocol for the management of patients with splenic injury at our hospital, we have managed significantly more patients with recognised splenic injuries non-operatively in the last 5 years, with only a few failures. In contrast, there has not been an increase in the number of spleens conserved at operation. Non-operative management may be appropriate as less severe splenic injuries are being detected associated with the increased use of ultrasound. Splenic injury is not a mandatory indication for laparotomy; non-operative management of splenic injuries should be considered in selected patients who are haemodynamically stable and can be closely monitored.

G/U 011

An audit of the use of critical care facilities in a district general hospital

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We report a retrospective audit of surgical activity on a six-bed HDU and a four-bed ITU from 1991 to 1995.

General surgical throughput has increased in our hospital during the study period, with an increasing proportion of vascular, gastrointestinal and hepatobiliary patients. We have noted a similar increase in the activity of the surgical HDU, and particularly an increase in the number of vascular patients admitted (n = 84, 16·1 per cent in 1991–92; n = 136, 23·8 per cent in 1994–95). Thirty per cent of HDU admissions are managed non-operatively. In 1991–92 6·9 per cent (n = 36) of patients were transferred to the ITU. Despite the increasing throughput, fewer patients needed this level of care in 1994–95 (3 per cent, n = 17). Average stay has fallen from 4·1 to 3·5 days, whilst the use of epidural and patient controlled analgesia has increased.

Surgical patients continue to comprise 45 per cent of ITU admissions. However, ITU admissions now constitute a smaller proportion of those who require high-dependency care (18·5 per cent in 1991–92, 14·8 per cent in 1994–95). Patients expected to survive based on admission scoring have increased from 18·8 per cent to 27 per cent (n = 18, n = 23 respectively), although only 5 of these patients were ventilated.

This study confirms that the HDU is essential in the management of patients following major surgery. It provides high-quality care, reduces the pressure on ITU facilities, and maximises the involvement of the surgeon in the postoperative period. Further work is needed to assess the admission criteria for both HDU and ITU to optimise care.

G/U 012

A health technology assessment of home parenteral nutrition for the treatment of intestinal failure

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Home parenteral nutrition (HPN) is used for the treatment of intestinal failure. A systematic review, quality of life/economic appraisal were performed. Sixty-four current patients (all with benign disease) were sent validated quality of life questionnaires, 51 agreed to take part. Quality of life scores were reasonable, but significantly lower ($P < 0{\cdot}05$) than the general UK population score. Older patients and those addicted to narcotics had the lowest scores. The cost to the NHS of HPN, at our institution, was ~£45 000 for the first year and ~£32 000 subsequently.

A systematic review of the literature revealed that catheter sepsis was the main complication (range 0·24–0·73 episodes per catheter year). Five per cent of Crohns patients per annum died of their underlying disease compared with 75 per cent of cancer patients and 93 per cent of AIDS patients. There was no evidence on costs, quality of life and effectiveness for HPN in patients with terminal malignant disease (TMD) or AIDS.

HPN for the treatment of 'benign' intestinal failure is expensive but life saving. It is associated with a reasonable quality of life and acceptable morbidity and mortality. The use of HPN for TMD or AIDS has to be questioned.

LGI 017

Pelvic side-wall brushings following rectal resection complement histological examination in predicting death

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Introduction: Histological examination of rectal resection specimens which reveal involved lateral resection margins (LRM) have been shown to be a predictor of local recurrence and death. Cytological examination of brushings of the pelvic side-walls following excision of the rectum may complement histological examination of the LRM.

Method: Cytological brushings were taken from 111 patients undergoing attempted curative rectal surgery between 1987 and 1989. The LRM of the specimens were examined and the cohort followed-up regularly for a minimum of 5 years.

Results: One patient had a villous adenoma, 4 died postoperatively and 6 were lost to follow-up and so have been excluded from analysis. Nine patients had both involved LRM and positive cytology. Twenty-nine patients had either involved LRM or positive cytology. Sixty-two patients had clear LRM and negative cytology. Six patients had Stage D disease and are excluded from further analysis.

Overall corrected 5-year survival was 54 per cent. Five-year survival was 33 per cent if cytology was positive and only 27 per cent if LRM were involved.

Discussion: Combined positive cytology and involved LRM had a greater sensitivity (88 per cent) in predicting death from rectal cancer than either modality on its own (66 per cent cytology and 73 per cent LRM).

LGI 018

How should patients with malignant colonic polyps be treated? A review of 60 cases

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Patients from whom a malignant large bowel polyp is endoscopically removed present a therapeutic problem. Should they be offered a surgical resection or kept under regular endoscopic surveillance? Thirty-seven men and 23 women [median age 74·5 years (range 60–86 years)] who had a polyp with at least a foci of invasive adenocarcinoma were identified. They were followed-up regularly in a dedicated colorectal clinic by clinical and endoscopic examination.

Fifty-eight malignant polyps were situated distal to the splenic flexure. Forty-nine patients were treated solely by endoscopic polypectomy. There was no local recurrence or death from colorectal cancer over a median follow-up of 49 months (range 5–126 months). Nine patients had surgical resections following polypectomy; in 3 cases it was technically impossible to remove the whole polyp endoscopically. In the other 6 patients there was no evidence of residual malignancy in the resection specimen. Over a median follow-up of 68 months (range 21–139 months) there has been no local recurrence. One patient died of disseminated peritoneal malignancy of unknown origin, there was no evidence of local recurrence on endoscopy. Another died from malignant change in a villous adenoma treated by radiotherapy, being unfit for surgery.

Patients with malignant large bowel polyps can be satisfactorily treated by local endoscopic removal avoiding the need for major surgery.

LGI 019

The outcome after multiple colorectal tumours

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There were 39 patients (average age 72·5 years) with synchronous tumours in 1009 patients with colorectal cancer treated by one surgeon between May 1980 and September 1995.

Twenty-seven (69·2 per cent) were diagnosed at operation, 6 (15·3 per cent) preoperatively and 6 postoperatively. All preoperative tumours were diagnosed at colonoscopy and 2 of the postoperative tumours. The other 4 postoperative tumours produced symptoms. There was an even distribution of tumours – 23 were right-sided, 19 were left-sided and 21 were rectal.

Twenty-eight operations (71·8 per cent) were curative and the most advanced stage of tumour were Dukes' A 5, Dukes' B 13 and Dukes' C 10. However, only 5 of these patients survived more than 5 years.

Patients with synchronous tumours do badly, with only 18 per cent surviving for more than 5 years.

There were 20 patients (average age 59·2 years) with metachronous tumours in this group of 1009 patients. 14 (70 per cent) had symptoms, 5 (25 per cent) were diagnosed at follow-up colonoscopy and 1 (5 per cent) had a rise in carcino-embryonic antigen.

The intervals to diagnosis were <5 years (9 patients), 5–10 years (5 patients) and >10 years (6 patients). The sites of the tumours were evenly distributed. Eighteen operations (90 per cent) were curative. There was no difference in Dukes' staging and all patients survived >2 years and 75 per cent survived >5 years.

LGI 020

An interactive, evidence-based, teaching system for use in the colorectal outpatient clinic using risk-estimation from a database of prior experience

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Introduction: Good clinical judgement depends on sound principles and extensive prior experience. Accurate, prospective collection of clinical data can provide statistically valid evidence on which to base clinical decisions and such data can also be used as a teaching tool for students and trainees who have limited clinical experience.

Method: Prospective collection of information concerning the presentation, clinical findings, investigation and outcome of all patients attending a colorectal outpatient clinic has been entered into a computer database since 1986. An interactive teaching system ('hot learning system', HLS) has been designed which uses the database to provide likelihood estimates for particular diagnoses (e.g. colorectal cancer) for real and hypothetical cases based on information provided by the user.

Results: Since 1986, complete records on over 6000 patients have been collected. The likelihood of finding a cancer in this population is 5 per cent and by using the HLS it can be demonstrated that this risk varies between 0 per cent and 30 per cent depending only on the age and presenting symptoms. By using a 'what if' approach, different investigation strategies (e.g. flexible sigmoidoscopy, barium enema) can be evaluated to ascertain their effectiveness in defined risk groups.

Conclusions: Live access to an extensive database of prior experience can provide the necessary clinical perspective to allow trainees to make informed decisions regarding the likelihood of finding serious pathology and the appropriateness of specific investigations. However, such a 'hot learning system' cannot make management decisions itself as it only provides statistical risk estimates based on a subset of the clinical information available to the doctor.

LGI 021

Apoptosis, p53 expression and prognosis in colorectal cancer

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Interest in the control of tumour growth has focused on the relationship between cell proliferation and cell death (necrosis and apoptosis). The protein product of p53 has a key role in inducing apoptosis. Normally, the turnover of the p53 protein product is rapid and the protein is not detectable by immunohistochemistry. If detected, it is probably mutant and non-functional.

The aims of the study were twofold: (a) to examine the relationship of apoptosis, mitosis and the expression of p53 mutant protein product in colorectal cancers, and (b) to evaluate their roles as prognostic factors, in conjunction with known prognostic indicators such as Dukes' stage and extramural vascular invasion. The tumours from 75 patients with colorectal cancer aged 45 years and under were staged using the Dukes' system. Apoptotic and mitotic counts, and the presence of extramural vascular invasion, were determined by light microscopy using standard criteria. The protein product of the p53 oncogene was determined using a streptavidin-biotin technique (CM1 antibody). Tumours were regarded as positive if there was a 10 per cent or greater staining of tumour nuclei.

A significant correlation was observed between apoptotic count and the mitotic index [$r = 0{\cdot}86$; $P = 0{\cdot}0003$ (Fisher's r to z)]. In addition, the mean apoptotic count was increased in tumours not expressing the p53 product (mutant protein), when compared with those in which it was detected [5·7 vs 4·3, $P = 0{\cdot}02$ (unpaired t-test)]. There was, however, no relationship between p53 expression and mitotic count. Independent risk factors (multivariate analysis) for overall survival were as follows: apoptotic count ($P < 0{\cdot}04$), Dukes' stage ($P < 0{\cdot}0001$), extramural vascular invasion ($P < 0{\cdot}02$) (Cox stepwise proportional hazards model).

This study has identified that apoptotic count is an independent prognostic indicator in colorectal cancer. Furthermore, these results suggest that p53 protein (functional) may have a key role in inducing apoptosis in these tumours. The possibility that restoration of p53 function may improve survival has implications for gene therapy of cancer.

LGI 022

Local recurrence after rectal cancer resection: any change over 20 years?

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It has been claimed that wider local excision of rectal cancer by anterior resection (AR) would lead to decreased local recurrence rates (LRR).

A consecutive series is reported of all operations for carcinoma of rectum by one surgeon over 20 years. For the first 10 years, before the recommendations for wider excision were made, results showed an overall LRR of 6 per cent (4/67) for abdomino-perineal resection (ARP) and 7 per cent (11/158) for AR. For the last 10 years, after wider local excision was adopted, the results for 'potentially curative' resections were 3 per cent (1/30) for ARP and 2 per cent (2/102) for AR. For 'palliative resections' over the same period LRR were 18 per cent (2/11) for APR and 23 per cent (14/64) for AR. The overall LRR for the last 10 years was 6 per cent (5/82) for APR and 8 per cent (14/66) for AR.

It is concluded that wide local excision has not altered the LRR for rectal cancer.

LGI 023

Long-term results of colectomy for idiopathic slow transit constipation

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Idiopathic slow transit constipation (ISTC) has been traditionally treated by subtotal colectomy and ileorectal anastomosis. Some authors have suggested a poor long-term outcome as patients complain of postoperative pain, bloating and laxative dependence, especially in those patients with preoperative pain. This study addresses the long-term success of surgery for idiopathic slow transit constipation. Patients were selected for surgery on the basis of (a) delayed transit; (b) life-long constipation; (c) normal videoproctogram and (d) absence of significant pain. Thirty patients with ISTC were assessed at a mean of 37 months after colectomy and ileorectal anastomosis.

Twenty-six patients had a successful outcome of no pain, normal evacuation and no laxative dependence. Four patients had a poor result due to postoperative pain and anismus (1) and intractable diarrhoea (2). Failures were obvious within 4 months of surgery. There were no later failures.

This study demonstrates that the application of strict selection criteria is associated with a good long-term outcome. In particular, the exclusion of patients with predominant pain prevents failures due to long-term pain.

LGI 024

Total anorectal reconstruction incorporating the electrically stimulated gracilis neoanal sphincter

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We investigated the feasibility and effectiveness of combining the electrically stimulated gracilis neoanal sphincter (ESGN) with a coloperineal anastomosis in selected patients following abdominoperineal excision of the rectum (APER).

Twelve patients underwent the procedure for carcinoma in 11 and melanoma in 1. The procedure was performed in stages. Stage 1 involved a conventional APER with the formation of a perineal stoma. In stage 2 the gracilis was mobilised, transposed around the anal canal and the stimulating equipment was implanted. Once muscle conversion was complete the defunctioning stoma was closed.

Eight patients had their stomas closed. The reasons for non-closure were death, perineal hernia, neoanal stenosis and inability to tolerate electrical stimulation. The motor action of the ESGN was measured using a water-filled balloon manometry system.

	Basal pressure (cm H_2O) ($n = 7$)	Maximum pressure (cm H_2O) ($n = 7$)	Functioning pressure (cm H_2O) ($n = 6$)
Start of electrical stimulation	30 (10–45)	122 (65–185)*	
After 1 year	22·5 (15–35)	76·2 (42·5–127·5)*	36 (30–90)*

Values are median (95 per cent confidence intervals) * $P < 0{\cdot}05$ Wilcoxon signed rank test.

All patients experienced some faecal soiling and difficulty in evacuation. Patients were satisfied with their function despite imperfect continence and none wished to go back to life with a stoma. The incorporation of the ESGN as part of total anorectal reconstruction results in a sustainable increase in neoanal canal pressure though modifications will be needed to achieve perfect continence.

LGI 025

Incidence, morbidity and obstetric factors in childbirth-related faecal incontinence

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The true incidence of faecal incontinence after vaginal deliveries is unknown. Physiological studies have identified sphincter damage and neuropathy in a high proportion of women after vaginal delivery particularly necessitating forceps extraction. We interviewed 906 women after childbirth (6–7 months after delivery). Thirty-six women (4 per cent) developed faecal incontinence for the first time after the index birth. There were 19 others who have recurrent or ongoing symptoms of incontinence. Stepwise regression analysis identified that only forceps delivery and vacuum extraction were an independent significant risk for incontinence. Twelve (33 per cent) of those with new incontinence had an instrumental delivery compared with 114 (14 per cent) of the 847 women who had never had faecal incontinence. Emergency Caesarian section did not protect against childbirth-related faecal incontinence; parity, age, episiotomy, second-degree tear, duration of labour, birth weight, head circumference and duration of gestation had no influence on the incidence of incontinence. Twenty-seven women said that symptoms occurred several times a week yet only 5 of them had consulted a doctor.

These studies indicate a 4 per cent incidence of faecal incontinence as an immediate consequence of childbirth which was significantly more common after forceps or vacuum extraction. Women in the United Kingdom with incontinence rarely seek medical attention.

LGI 026

Endoanal sliding flap advancement for high fistula *in ano*

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Between 1989 and 1995, 19 endoanal advancement flaps were fashioned to treat high anorectal fistulas. Active sepsis was initially treated by drainage and insertion of a seton. Repair was undertaken 2 months later. The primary tract was cored out: the internal sphincter repaired if appropriate and a broad-based flap of mucosa with internal sphincter advanced.

Patients and results (mean follow-up 38 months)

Condition	Primary tract	Recurrence
Crohn's	1 RVF, 2 extra sphincteric	1*
UC	1 RVF	
Obstetric injury	3 RVF‡	
Crypto-glandular	2 extrasphincteric	
Crypto-glandular	1 suprasphincteric	
Crypto-glandular	9 high transphincteric†	2**

†One with concomitant sphincter repair. ‡Two with sphincter repair.
*Symptomatically improved.
**One lost to follow-up/one successful second repair.

Conclusion: Success depends on the preliminary elimination of active sepsis and on ensuring flap viability. It is concluded that flap advancement is an effective method of repair in high fistula *in ano*. It minimises perineal wounds (and time off work) and maximises continence by preserving both external and internal sphincters. Consideration should be given to maximal preservation of sphincter function in all fistulas *in ano* by extending the indications for endoanal flap advancement to low fistulas.

LGI 027

Prospective evaluation of contrast enhanced magnetic resonance imaging in the evaluation of fistula *in ano*

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The key to the successful management of fistula *in ano* lies in identification of the relationship of the primary track to the anatomical structures through which it passes, and of additional tracks and abscesses which may prevent resolution of the primary track.

We prospectively compared a specifically developed dynamic contrast-enhanced magnetic resonance imaging (MRI) sequence with digital rectal examination, operative findings and long-term follow-up in the evaluation of primary fistula tracks, secondary tracks and abscesses in 42 consecutive patients with a suspected diagnosis of fistula *in ano*.

Contrast enhancement shows granulation tissue as a high signal intensity which clearly highlighted active fistula tracks against the control T1 weighted images. There were five discordances between MRI and surgery in the identification of primary tracks: MRI showed an ischio-rectal abscess and tracks with no enteric connection in one patient who at operation had an epithelialised primary fistula. Four patients with fistulae on MRI had no enteric opening found at surgery and were treated as sinuses. Long-term follow-up has shown failure to heal in all four patients and further surgery has confirmed fistulas in the sites predicted by MRI.

When compared with final outcome measures (as opposed to surgical findings alone) MRI had a 97 per cent sensitivity and 100 per cent specificity in the detection of fistula. MRI also identified more secondary tracks and was more accurate at identifying complex fistulas than either digital rectal examination alone or surgical exploration.

LGI 028

Function and quality of life after successful restorative proctocolectomy

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We have assessed 98 patients after pouch construction using a 12-point score, quality of life assessment and a satisfaction index. Functional results were classified as good (score 0–3) 40 per cent, moderate (score 4–6) 31 per cent and poor (score >6) 29 per cent. The most frequent imperfections were urgency (56 per cent), dietary restriction (54 per cent), anti-diarrhoeal agents (52 per cent), nocturnal soiling (49 per cent), more than one nocturnal evacuation (44 per cent), impaired discrimination (35 per cent), episodes of incontinence (27 per cent), day-time frequency greater than 7 (24 per cent) and the need to wear pads at night (22 per cent).

The factors related to poor function (high score) were: (1) Crohn's disease ($P < 0{\cdot}01$), (2) sutured ileoanal anastomosis; soiling ($P < 0{\cdot}01$), (3) postoperative pelvic sepsis ($P < 0{\cdot}02$) and (4) pouchitis ($P < 0{\cdot}05$). Age, pouch design, operative difficulty, loop ileostomy, postoperative fistula or obstruction had no significant impact on function. Seventy-two per cent considered their quality of life was better than before the operation, 87 per cent said the pouch was worth the effort and 73 per cent said that they would definitely recommend the operation to a friend; only 16 per cent regretted having the operation. There was a close correlation between function and satisfaction ($P < 0{\cdot}001$). Elderly patients were more frequently dissatisfied. There was a close correlation between function and social activity score ($r = 0{\cdot}58$).

Posters 1–88

Breast

Poster 001

Prospective evaluation of stereotactic FNAC performed on impalpable breast lesions

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Stereotactic FNAC of clinically occult breast lesions is regarded as an accurate diagnostic modality which reduces the requirement for open surgical biopsy.

A prospective study of the results of stereotactic FNAC was performed over a two-year period on 128 consecutive patients with screen-detected impalpable breast lesions with an uncertain or suspicious radiological appearance. Unsatisfactory FNACs were repeated if necessary. Lesions were excised if considered mammographically or cytologically suspicious. The non-operative group was followed up clinically for a minimum of three years.

One hundred and fifty-four stereotactic FNACs were performed: 40·4 per cent and 27·3 per cent were considered unsatisfactory (C1) in the first and second year respectively and the results were corrected for this. Fifty-four patients underwent open biopsy. A summary of the results is shown below:

Investigation	Sensitivity	Specificity	Corrected sensitivity	Corrected specificity
Initial FNAC	77 per cent	91 per cent	53 per cent	61 per cent
Initial FNAC + repeat	74 per cent	91 per cent	53 per cent	56 per cent

The combination of stereotactic FNAC and mammography achieved a 100 per cent accuracy for the diagnosis of screen-detected impalpable breast lesions, with no cancers being detected in the non-operative group during follow-up. Initial satisfactory stereo FNAC would not have detected 23 per cent of cancers. This inaccuracy increases to 47 per cent if the unsatisfactory samples are considered.

For the accurate diagnosis of impalpable breast lesions the results of stereotactic FNAC and the mammographic appearance must be considered together.

FNAC = Fine Needle Aspiration Cytology.

Poster 002

An assessment of the cost-effectiveness of investigations in early breast cancer

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Investigations performed in breast cancer management are expensive. Screening for metastatic disease is performed in routine patient management irrespective of the stage of the disease. A retrospective analysis of 170 proven breast cancer for all stages of disease compared the results of fine needle aspiration cytology (FNAC), mammography (Mam), isotope bone scan (IBS), liver ultrasound scan (USS) and chest X-ray (CXR) for 'early' (<T2, N0, M0) (n = 110) and 'advanced' (>T2, N0, M0) (n = 60) disease, with a view to their role in cost-effective management.

The results revealed an acceptable role for FNAC (79 per cent, 87 per cent) and Mam (51 per cent, 90 per cent) respectively in both early and advanced disease. USS, IBS and CXR provided no additional information in early disease (0 per cent, 2 per cent, 0 per cent) at a cost of £206 per patient (2 per cent represented false positives). A recent recommendation has suggested a role for specialized breast clinics treating over 150 cases of breast cancer per 300 000 population. Assuming 65 per cent of cases to be early cancer and the need for cost-effective patient management, cost savings for clinicians and trusts would be £20 085 per annum.

Poster 003

Oestrogen receptor status predicts local recurrence after breast conservation surgery

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Oestrogen receptor status is a recognised prognostic indicator in breast cancer. However, less is known of its relationship to local recurrence following breast conservation surgery. We have addressed this question in a retrospective study of 282 patients treated, for early breast cancer, by lumpectomy between 1984 and 1991.

Conservation surgery was augmented in most cases by adjuvant therapy; radiotherapy, with or without tamoxifen, or tamoxifen alone. Oestrogen receptor status was estimated routinely by a ligand-binding method, cut off 20 fmol/mg, where unavailable immuno-histochemical assessment of paraffin blocks was arranged. Tumour size and nodal status were recorded by the examining pathologist. Incidence of local recurrence was noted from case sheets. The minimum period of follow-up for surviving patients was 3·5 years. Multivariate analysis shows oestrogen receptor negativity provided the best independent predictor of local recurrence ($P < 0{\cdot}00005$) and tumour size also an independent predictor ($P = 0{\cdot}0001$). Adjuvant radiotherapy and tamoxifen are both independent predictors reducing the incidence of local recurrence ($P = 0{\cdot}006$ and $P = 0{\cdot}0005$ respectively).

Thus oestrogen receptor status appears to provide an indication of the risk of local recurrence after breast conservation. Preoperative assessment, by fine needle or tru-cut biopsies, could influence the decision to opt for this form of surgery.

Poster 004

Type I tyrosine kinase receptors as targets for therapy

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Over-expression of the EGF and C-erbB-2 coded receptors are associated with poor prognosis in breast cancer. Both have been considered as targets for tumour therapy. However present methods of receptor estimation are deficient, making elucidation of receptor function difficult. We have developed a quantitative immunohistochemical method of receptor measurement and have applied this to a series of over 100 breast tumours.

We find C-erbB-2 over-expression in 91 per cent of cancers, considerably higher than the normally reported rate. Conversely, in 97 per cent of breast cancers, EGFR expression is considerably lower than normal breast. Our series reveals a clearly evident and previously unreported bimodal distribution of C-erbB-2 expression. Fluorescent *in situ* hybridisation shows the second mode (21 per cent) is associated with gene amplification but suggests an alternative mechanism of over-expression in the first. Within the first mode (79 per cent) expression is up to 19 times normal. Chi-square analysis shows over-expression of 6 times normal correlates with lymph node status (P = 0·029) with a trend evident for tumour stage (P = 0·086).

Thus EGFR appears to be a poor target for tumour-specific therapy, but C-erbB-2 shows greater promise. This sensitive assay raises the possibility that the clinically significant level of C-erbB-2 expression is below that defined by amplification.

EGF = Epidermal Growth Factor.

Poster 005

Use of image-guided core biopsy in patients with breast disease

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Triple assessment by clinical examination, radiology and cytology is now firmly established in the appraisal of patients with breast disease. If the findings of the triple assessment are in accord, firm management recommendations may be made, otherwise surgical biopsy is usually required to establish the diagnosis.

The use of image-guided core biopsy may diminish the need for such biopsies. We have used this technique since August 1994 and we report our experience gained to date.

Ninety-two patients have undergone the procedure, 88 of whom have been ultrasound-guided and 4 stereotactic. The indications for core biopsy were discord between clinical/radiological findings and cytology (65 patients), inadequate cytology (18 patients) or as a preferred alternative to cytology (9 patients).

A diagnosis of malignancy was established in 39 of the 92 patients and 30 patients were discharged with a benign diagnosis. The remaining 23 patients required surgical biopsy, 11 of which were malignant and 12 benign. This latter group includes 9 patients who elected to have surgery despite a benign core biopsy.

Our experience with image-guided core biopsy suggests that it can reduce the need for surgical biopsy, with benefit both to the patient and to overstretched hospital budgets.

Poster 006

Can axillary node status index (ANSI) replace pathological nodal status in the management of breast cancer?

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Integrins are transmembrane receptors that regulate cell-matrix adhesion, each consisting of an α and a β subunit. Reduced integrin expression in primary breast cancer is related to the presence of axillary metastasis. This study seeks to determine if the integrins could be used in a clinical score to predict nodal status.

A retrospective study was performed using primary breast cancer sections of 46 LN+ and 55 LN− women with a mean tumour size of 2·5 (0·5–9·0) cm. Loss of the $\alpha1$, $\alpha2$, $\alpha3$, $\alpha6$ αv, $\beta1$ and $\beta5$ subunits were related to nodal status using the χ^2-test. Of these subunits, the best indicator of positive nodal status was $\beta1$ with a sensitivity of 72 per cent and specificity of 85 per cent. When combined with standard tumour variables analysed using logistic regression with node status as the end point, loss of the $\beta1$, αv and $\alpha2$ integrins, tumour size >2 cm, the presence of vascular invasion and multifocal disease were selected as the most potent indicators. Each variable that predicted LN+ status was given a score of 1, while the same variable to predict LN− status scored 0. A summed score of 6 thus strongly predicted LN+. ANSI was compared to node status determined by histology and immunostaining (CAM 5·2).

	True axillary nodal status (number of women)	
Score	Lymph node positive (n)	Lymph node negative (n)
6	3	0
5	17	0
4	14	0
3	7	9
2	2	17
1	2	17
0	1	12

A high ANSI score allows accurate prediction of axillary nodal status in human breast cancer and might enable patient selection for axillary surgery and/or adjuvant therapy.

(Key: LN+ lymph node positive; LN− lymph node negative.)

Poster 007

pS2 expression adds prognostic information to node status for 5-year survival in breast cancer

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Prognosis in breast cancer reflects the presence of axillary node metastasis at the time of diagnosis. Expression of pS2, an oestrogen-regulated gene, is associated with a good short-term prognosis and response to endocrine therapy. The aim of this study was to determine whether pS2 gene expression added useful information to node status for survival at 5 years.

pS2 expression was determined using the northern blot technique to detect pS2 messenger ribonucleic acid (mRNA) in tumour tissue from 90 patients with primary, previously untreated, breast cancer. Axillary node status was established by axillary node sampling or clearance, and follow-up continued for at least 5 years or until death.

At 5 years, 26/90 (29 per cent) patients had developed recurrent disease and 19 (21 per cent) of these had died from breast cancer. Axillary node metastasis, detected in 44/90 (49 per cent) patients at diagnosis, was significantly associated with poor prognosis (P = 0·002, Fisher's exact test). pS2 mRNA expression, present in 27/90 (30 per cent) cancers was strongly associated with survival at 5 years (P < 0·001, Fisher's exact test).

The combination of node status and pS2 expression defined patients with particularly good prognosis (node negative, pS2 positive; no mortality at 5 years) or poor prognosis (node positive, pS2 negative; 50 per cent mortality at 5 years). Evaluation of pS2 expression may provide additional prognostic information to node status at diagnosis.

Poster 008

Positive cavity shavings in relation to tumour size and histological grade

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The incidence of local recurrence after lumpectomy for breast cancer is reported to be 7–32 per cent. Most recurrences occur close to the primary excision site, suggesting that they represent residual disease rather than true recurrence. Previous reports of re-excision or cavity shavings have revealed 30–38 per cent incidence of residual disease.

The aim of this study was to determine whether or not tumour size and histological grade were related to a higher incidence of residual disease in the cavity shavings.

An analysis of 138 consecutive patients treated by lumpectomy was performed. Shavings were taken from the cavity wall for histology.

Modified Bloom and Richardson classification was used to determine the histological grade. Results are as follows:

	Grade I	Grade II	Grade III
Shavings + VE	4 (17 per cent)	21 (49 per cent)	12 (55 percent)
Shavings – VE	20 (83 per cent)	22 (51 per cent)	10 (45 per cent)

	Size <2 cm	Size >2 cm
Shavings + VE	28 (37 per cent)	14 (66 per cent)
Shavings – VE	47 (63 per cent)	7 (34 per cent)

Conclusion: Tumour size and pathological grade can predict the likelihood of the residual disease after local excision. This can identify a group of patients who are potentially at a higher risk of local relapse following conservative surgery.

Poster 009

Colour flow Doppler in assessment of malignant breast disease

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Colour flow Doppler (CFD) is a sensitive modality for detection of disordered blood flow in malignant breast lesions.

CFD was undertaken in 20 patients with malignant breast disease, median age 59 (40–85), and compared to mammography, cytology (FNAC), histology, and lymph node involvement. Patients underwent radial scans using an ATL Doppler with 7·5–13 MHz linear array transducer. Scans were graded blind by video analysis to give a CFD index (CFI) of 0–4 for malignancy, based on enhanced colour flow intensity, abnormal flow patterns, and peak systolic velocities. The normal breast was used as control.

Abnormal flow was detected in all patients (sensitivity 100 per cent). CFD detected 3 diffuse tumours in which mammography was negative or equivocal. Increased flow (CFI-1) in a patient with previous excision of a medullary carcinoma detected local recurrence, unconfirmed by FNAC/mammography. Correlation of tumour sizes determined by CFD with histology ($r = 0{\cdot}97$), was closer than that derived by mammography ($r = 0{\cdot}85$). In one elderly patient with infiltrating lobular carcinoma, CFI decreased from 3 to 2 following 4 months treatment with tamoxifen. In a further patient, involution of a T3N0M0 tumour following neoadjuvant chemotherapy was reflected by loss of abnormal blood flow, and return of CFI to 0.

CFD is a sensitive modality to complement mammography and FNAC in assessment of breast malignancy. It may also have a role in assessment of physiological effects of adjuvant therapy on tumour neovascularisation.

Endocrine

Poster 010

Surgical anatomy of the parathyroid glands in secondary hyperparathyroidism

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The anatomical location of parathyroid glands that are hyperplastic secondary to renal failure may differ from the normal situation. This study presents a prospective analysis of parathyroid anatomy in a series of patients undergoing parathyroidectomy for renal hyperparathyroidism.

The anatomical positions of 241 hyperplastic parathyroid glands were recorded in a consecutive series of 60 patients undergoing neck exploration for secondary hyperparathyroidism. Four patients had fewer than 4 glands identified, 51 patients had 4 glands, and 5 patients (8 per cent) had supernumerary glands.

Upper parathyroid glands were found to be located: in an area 2 cm in diameter centred just above the intersection of the recurrent laryngeal nerve (RLN) and the inferior thyroid artery (ITA) ($n = 91$, 77 per cent), adjacent to the upper pole of the thyroid and its vessels ($n = 13$, 11 per cent), below the RLN/ITA intersection ($n = 8$, 7 per cent), para-pharyngeal or para-oesophageal ($n = 4$, 3 per cent), in the carotid sheath ($n = 1$) and intrathyroidal ($n = 1$).

Lower parathyroid glands were found in close relation to the lower pole of the thyroid ($n = 69$, 56 per cent), in association with the thyrothymic ligament ($n = 35$, 28 per cent), in the mediastinum ($n = 11$, 9 per cent), below the intersection of the RLN/ITA ($n = 4$, 3 per cent), undescended ($n = 2$) and intrathyroidal ($n = 2$). Ninety-eight of the 118 upper glands (83 per cent) demonstrated quite close symmetry of position. In contrast this feature was only recognised in 72 of 123 lower parathyroid glands (59 per cent).

The anatomy of hyperplastic parathyroid glands demonstrates important differences in comparison with normal glands studied at autopsy. The data presented have been used to formulate a logical plan of dissection in patients with secondary hyperparathyroidism.

Poster 011

Cervical exploration for primary hyperparathyroidism – a 25-year experience

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We reviewed our experience of cervical exploration for primary hyperparathyroidism (PHPT) between 1970 and 1995. Of 214 patients identified, adequate records were available for 175 (81 per cent). Modes of presentation included urological (22 per cent), skeletal (11 per cent), gastrointestinal (7·4 per cent), psychiatric (10·3 per cent) symptoms and mixed (27 per cent). Twenty-four per cent of patients were asymptomatic. There was no association between the presence or absence of symptoms and preoperative serum calcium levels. Fifty patients (29 per cent) had a total serum calcium level greater than 3·0 mmol/l, 106 (62 per cent) had a level between 2·6 and 3·0 mmol/l and 16 (9 per cent) had normal levels. Pre-operative imaging was performed in 23 per cent of patients. Ultrasound scanning was used in 16 per cent. CT scan (2 per cent) and radionuclide imaging (5 per cent) were used in patients with previous neck surgery.

Pathological findings were a single adenoma (85 per cent), two adenomas (2 per cent), hyperplasia (11 per cent), carcinoma (2 per cent) and in one case normal parathyroid tissue. Postoperatively 106 (60 per cent) patients developed hypocalcaemia; this was transient in 97 (91·5 per cent) and permanent in 9 (8·5 per cent) patients. Calcium supplementation was required in 13 of those with transient and all with permanent hypocalcaemia. Permanent normocalcaemia was achieved in 166 (95 per cent) of patients after a single exploration. Repeat exploration was required in 3 patients (1·7 per cent) with persistent hypercalcaemia. Five (2·8 per cent) patients developed postoperative complications: infected haematoma (1 patient), chest infection (2 patients), vocal cord paralysis (1 patient), hoarseness with normal vocal cords (1 patient). Cervical exploration for PHPT is a highly successful procedure with a low complication rate. All patients with PHPT should be offered cervical exploration.

Vascular

Poster 012

Endoluminal repair of large aortic aneurysms: a pilot study

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Purpose: To check feasibility of the 'Bray' technique for repair of infrarenal aneurysms >5·5 cm.

Methods: Repair was attempted in 10 patients (9 male), median age 67 years (65–78). The technique is based on the Parodi method, but pre-expanded PTFE and Palmaz stents form the stentgraft which is deployed over an appropriate sized balloon over an extra-stiff guide wire introduced via a Bray sheath – 18 or 24F – through the femoral artery. Fixation was to the aorto-iliac segment in 7, aorto-aortic in 2 and ilio-iliac in 1.
Results: Failure occurred in the first 3 for technical reasons, and open repair was carried out without complication. In 7 success was achieved, but in 2 the lower stent slipped necessitating open repair. Five patients left hospital with functioning grafts. One has a small leak from the upper stent, 1 developed a graft infection 6 months postop. and in 1 the lower stent pulled out necessitating open repair after 3 months. Two high-risk patients presenting with rapidly expanding aneurysms died within 30 days of open surgery. No patient died from the endoluminal procedure. The outstanding problem of slippage of the lower stent has been solved.

We conclude that the Bray method is feasible for large aneurysm repair, and further developments are justified.

Poster 013

3-D spiral C-T reconstruction compared with angiographic estimates of abdominal aortic aneurysms – of size and shape

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Purpose: To validate 3-D reconstruction of spiral C-T estimates of aortic size and shape for planning of stentgraft, balloon and sheath sizes for endoluminal grafting.
Method: Twenty-six patients underwent 3-D reconstruction of their aneurysms. Images of the first 7 patients undergoing endoluminal repair were compared with peroperative measurements of neck length and diameter, cuff length and diameter and the required prosthesis length.
Results: In 26 patients the median neck diameter was 22 mm (16–30), neck length 26·5 mm (7·9–55), A-P diameter 55·9 mm (40–70); 11 had cuffs free of clot and <30 mm diameter with a median diameter of 24 mm (15–29) and a cuff length of 14·5 mm (4–60). In 7 patients undergoing endoluminal repair, measurements using the 2 methods are shown in the Table.

Method	Neck length	Neck diam.	Cuff length	Cuff diam.	Prosth. length
C-T	21 (22·75–38·3)	23 (22·0–26·0)	12 (5·8–17·3)	21·5 (16·8–24·3)	140 (116·3–178·8)
Angio	22 (22·3–32·8)	21 (21·5–26·5)	13 (6·3–18·8)	20·5 (15·8–23·3)	130 (109·3–159·8)
Rho	0·99	0·85	0·99	0·99	0·96
P	0·02	0·04	0·02	0·03	0·02

All values expressed in mm as medians (range). Rho = Spearmans Corr.

Conclusion: C-T with 3-D allows selection of aneurysms with suitable geometry for endoluminal repair, and enables accurate planning of stent-graft size and shape.

Poster 014

Who should perform lower limb amputations? Limitations of junior surgeons

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The aim of this study was to determine the factors which predict independent ambulation following major limb amputation. Over a 4-year period, 172 patients underwent 193 lower limb amputations (86 AKA, 98 BKA and 9 through knee) for peripheral vascular disease. The stump revision rate was 13·5 per cent and was significantly more frequent in patients having a prior vascular reconstruction, but the level of amputation was unaffected. Overall, 110 patients were deemed to be unsuitable for prosthetic limbs (32 per cent died, 32 per cent wheelchair independent, 17 per cent tertiary referrals, 12 per cent bilateral), whilst 62 patients were referred to the DSC.

The walking rate for patients considered for limb fitting was 72 per cent. Univariate analysis suggested that independent ambulation was not affected by patient age, mode of presentation (rest pain or gangrene), the presence of ischaemic heart disease, diabetes, smoking status, previous surgical revascularisation or the level of amputation. However the grade of surgeon performing the amputation did appear to infuence long-term outcome, see below.

	Junior trainees	Senior trainees + consultants
Diabetics (per cent)	53	35
Smokers (per cent)	33	38
IHD (per cent)	30	19
Gangrene (per cent)	63	50
Previous reconstruction (per cent)	80	63
Stump complications (per cent)	50*	25*
Independent ambulation (per cent)	60*	85*

* $P < 0.05$ Chi-squared test.

These results suggest that independent ambulation following amputation is determined by the incidence of stump-related complications, which is in turn related to the seniority of the operative surgeon. In patients deemed suitable for ambulatory training following amputation, the operation should be performed by a senior trainee or consultant.

Poster 015

General surgery with a special interest in vascular surgery: is separation inevitable?

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In order to define any changes in the nature of workload of a general surgical firm with a vascular interest, three prospective three-month audits have been carried out. The audits were undertaken in 1989, 1990 and 1995. A note was made of out-patient referrals, admissions and operations performed.

By 1990 the annual number of arterial reconstructions had risen to an annual level of approximately 140 cases per year. This remained stable up to and including 1995.

The total number of out-patient referrals was 277 and 281 in audits one and two respectively. By 1995 there had been a 30 per cent increase in patients referred. The number of general cases fell but vascular cases including varicose veins rose. Thus in 1989 approximately half of the patients referred were general surgical; this number had fallen to one quarter by 1995.

The total number of patients admitted to the unit in the three audits remained more or less constant at about 300. The number of patients with varicose veins rose due to the waiting list initiative. The largest group of patients throughout were those admitted as general surgical emergencies. The number of general surgical operations fell steadily through audits one to three. The number of arterial and varicose vein operations rose from one third of total in 1989 to more than half by 1995. Overall the number of operations performed remained fairly constant at approximately 220.

The dramatic rise in the number of arterial out-patient referrals with a corresponding fall in general surgical cases shows that the general surgical component of the firm is being maintained largely due to the emergency commitment. Any circumstance which results in a fall in the number of general surgical emergencies will effectively separate vascular surgery from general surgery.

Duplex alone as a diagnostic test for management of lower limb ischaemia

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Intra-arterial arteriography is often regarded as the recommended investigation for deciding the treatment options for patients presenting with lower limb ischaemia. Duplex has been shown to be an accurate method for non-invasive and inexpensive assessment of arterial disease. This study was designed to compare the decisions based on duplex with those on arteriography.

The arteriograms of 60 patients (38 males), median age 73 (range 45–95), presenting with lower limb ischaemia (intermittent claudication in 25, rest pain in 10, tissue loss in 24, 1 popliteal artery aneurysm) were reviewed blind by a single consultant vascular surgeon. A management plan was devised for each, this being operative (type), radiological or conservative. This was repeated 1 week later, again blinded, without knowledge of the arteriography, with duplex records.

The management plans in 55 (92 per cent) cases were in agreement based on duplex and arteriography.

	Arteriogram based			
Duplex based	Operative	Radiological	Conservative	Totals
Operative	28	2	0	30
Radiological	0	19	2	21
Conservative	0	1	8	9
Totals	28	22	10	60

Exact agreement = 92 per cent, Kappa = 0·87 (>0·8 = high agreement).

In 3 of 5 cases where a difference in management was suggested, it was felt that duplex provided better management in light of the actual findings and outcome.

This study demonstrates a high level of agreement in management based on duplex with that based on arteriography in lower limb arterial disease, this suggesting that operative procedures can safely be performed based on the results of duplex examination alone.

Poster 017

Arm–thigh PVRTF predicts a pressure drop over iliac stenoses

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The aorto-iliac arterial segment remains difficult to assess accurately by non-invasive means. Pulse Volume Recording Transfer Function (PVRTF) is a new non-invasive vascular technique.

Pulse volume waveforms are collected from an arm cuff (PVL 50, Scimed, UK) and a frequency response curve (input) is derived. A similar curve (output) is generated from a thigh cuff at the groin. Division of these curves produces a transfer index.

PVR transfer index predicts aorto-iliac occlusions and stenoses when compared to biplanar arteriography and colour flow duplex. In this study we wished to compare this index with intra-arterial pressure measurements in patients with iliac artery stenoses.

Nineteen patients yielded 20 iliac segments with suspected iliac stenoses on colour flow duplex examination. Each was then assessed with PVRTF and intra-arterial pressure measurements.

Intra-arterial pressure drop	Number	Mean PVRTF index	Standard deviation
Significant	11	0·86*	0·12
Not significant	9	0·99*	0·08

* Groups are different at the 95 per cent confidence interval.

Arm–thigh PVRTF is able to predict pressure drops across iliac stenoses.

Poster 018

MMP-9 is elevated in acute wounds but not venous ulcers

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Matrix metalloproteinases (MMPs), a family of extracellular matrix degarding enzymes, are expressed during cutaneous wound healing. Elevated levels of MMP-9 (gelatinase B) have been associated with wound fluid from chronic wounds. The aim of this study was to examine tissue MMP-2 and -9 (gelatinase A and B) in acute wounds and venous ulcers.

A total of 42 biopsies from eight acute granulating surgical wounds and 30 biopsies from six venous leg ulcers were taken from the edge and base of the wounds at two-weekly intervals during healing. Normal skin from the patients with acute wounds was used as a control. Tissue gelatinase activity was demonstrated by gelatin zymography. Bands of gelatin digestion consistent with MMP-2 and -9 were analysed using scanning laser densitometry with volume/intensity analysis.

	Acute wounds	Venous ulcers	Normal skin
MMP-9	62 (5·3)*	20·8 (7·4)	12·5 (5·5)
MMP-2 (72 kDa)	35·9 (3·6)	18·9 (3·7)†	40 (7·6)
MMP-2 (66 kDa)	35·9 (3·2)*	33·7 (6·6)	7·2 (4·7)

Arbitrary units of laser transmission/μg protein. Mean (SEM). * $P < 0·001$, † $P < 0·05$ vs normal skin (Mann–Whitney U-test).

Contrary to the results of previous studies, we have shown that MMP-9 activity in venous ulcers is lower than that seen in acute wounds.

Poster 019

Can lower limb colour-coded duplex safely replace diagnostic arteriography?

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As a result of technological advances and increasing operator expertise, it is now possible to map out the arterial tree in many patients with lower limb arterial disease. We, therefore decided to abandon diagnostic arteriography in favour of colour-coded duplex as the first-line investigation of lower limb occlusive arterial disease, and the purpose of this study was to assess the safety and efficacy of this approach. Over a one-year period, 423 consecutive limbs have been assessed from aorta to ankle by duplex scanning. The indication for investigation was claudication in 75 per cent, rest pain in 15 per cent and tissue loss in 10 per cent.

Duplex examinations were technically successful in 394 (93 per cent) limbs, with the failures due to inability to insonate the iliac arteries in 3 limbs (0·5 per cent) and calf vessels in 26 (6·5 per cent) limbs. On the basis of duplex findings, 12 limbs were referred for diagnostic arteriography because of an inadequate duplex examination, 170 (40 per cent) were managed conservatively, 201 (48 per cent) limbs were referred for angioplasty, and 40 (10 per cent) underwent surgical intervention. There was an unexpected finding in only 5/201 (2 per cent) limbs referred for angioplasty and in only 9/86 (10 per cent) limbs with SFA occlusions was there disagreement concerning the presence or absence of an SFA stump. There were no unexpected findings in those referred for surgery.

We conclude that colour-coded duplex scanning can replace diagnostic arteriography in up to 98 per cent of patients with lower limb arterial disease and that patients can be safely referred for either angioplasty or reconstructive surgery on the basis of duplex findings alone.

Poster 020

Prospectively randomised trial of 1 versus 6 weeks of compression after sclerotherapy for varicose veins

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Fegan described 6 weeks of compression bandaging following injection sclerotherapy but many surgeons (and patients) do not adhere to this. A prospectively randomised trial of 1 versus 6 weeks of compression was performed in 111 limbs (100 patients) to assess recurrence, complications and patient satisfaction. Reflux was determined by duplex. One hundred and ten injection sites in 54 limbs underwent 1 week of compression, all tolerating bandaging well; 120 injection sites in 57 limbs underwent 6 weeks of compression, 9 (15·3 per cent) being unable to tolerate bandaging fully. Follow-up was complete at 3 months in all cases, in 109 limbs (98 per cent) at 12 months and in 83 limbs (75 per cent) at 36 months.

Complications (staining, pain, phlebitis, blistering, ulceration or induration) occurred at 32/110 sites after 1 week of compression and 32/120 sites after 6 weeks ($\chi^2 = 0{\cdot}07$, $P = 0{\cdot}79$). Recurrence of varicosities was noted in the 1-week group in 18/110 (16·4 per cent), 28/101 (27·7 per cent) and 27/79 (36·7 per cent) at 3, 12 and 36 m respectively, and in the 6-week group in 20/120 (16·7 per cent), 38/117 (32·5 per cent) and 39/86 (45·4 per cent) (χ^2 NS, all times). Major reflux was associated with recurrences at 40/76 sites compared with 32/97 in systems without reflux ($\chi^2 = 5{\cdot}98$, $P = 0{\cdot}014$). Satisfaction: Patients were dissatisfied with 43 limbs (38·7 per cent) but with no difference between the two groups. Recurrence was the major reason for dissatisfaction.

Conclusion: The use of a short 1-week compression after sclerotherapy is better tolerated and gives equivalent results. Recurrence of varicosities is, however, relatively common and a significant number will suffer troublesome complications.

Poster 021

Is Duplex surveillance of PTFE grafts worthwhile?

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Following infra-inguinal bypass with polyfluorotetraethylene (PTFE), patients were entered into a prospective graft surveillance programme using colour duplex, clinical examination and ankle–arm pressure measurements carried out at regular intervals.

Two hundred and twenty grafts (141 above-knee popliteal, 69 below-knee popliteal, 10 tibial) were patent on discharge from hospital and entered into the graft follow-up programme, with a total of 560 duplex scans (median 2 scans/graft, range 1–8). An intervention to maintain graft patency based on ultrasound findings was carried out in 10 patients: 4 for anastomotic disease and 6 for disease in proximal and distal vessels. Two of these grafts subsequently occluded at 8 and 40 months.

Thirty-five grafts (16 per cent) occluded despite apparently normal duplex scans, resulting in 18 amputations. The median time between the last normal duplex scan and graft occlusion was 6 months (range 1–62 months).

Twenty-six grafts (12 per cent) were found to be occluded unexpectedly on routine scanning, without any clinical deterioration. At 36 months primary graft patency was 48 per cent and secondary patency was 51%.

If the aim of graft surveillance is to identify bypass grafts at risk of occlusion, the present study suggests that regular postoperative duplex scanning of PTFE grafts is not justified.

Poster 022

Difficult leg ulcers: does inpatient management have anything to offer?

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Despite adequate compression therapy, some leg ulcers are slow to heal. This may be due to poor patient compliance, an ischaemic component to the ulcer, or rarely malignancy. Does a period of inpatient management improve the healing rate and outcome for these patients?

From 1990 to mid 1995 there were 122 admission (99 patients) of patients with intractable or deteriorating leg ulcers. Only 45 ulcers (45 per cent) were purely venous in origin, malignant change was present in 7 (7 per cent), and arterial disease the predominant cause in 12 (12 per cent). The median duration of stay was 36 (range 1–302) days.

Arterial inflow was improved in 19 patients, 15 required venous surgery, 47 had skin grafts and 9 came to amputation. Conservative management alone was used in 29 patients. Those patients who had a skin graft were more likely to leave hospital with a healed ulcer (22 patients, 43 per cent) than the group as a whole (30 patients, 25 per cent, $P = 0{\cdot}0001$, Chi-squared test). Despite maximum treatment 77 (63 per cent) left hospital unhealed and recurrence in the first month after discharge was frequent.

Inpatient treatment does have a place in the management of difficult ulcers but recurrence rates remain high, particularly if the underlying abnormality is not corrected. Not all ulcers can be healed.

Poster 023

Increased microvascular oxygen supply to areas of ulcerated skin in the lower limb suggests the existence of poor oxygen diffusion conditions

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The microvascular blood flow and oxygen supply in skin bordering leg ulcers of various aetiologies (ischaemic, venous and diabetic neuropathic) was assessed in a total of 11 patients using the non-invasive techniques of laser Doppler flowmetry, transcutaneous oximetry and micro-lightguide spectrophotometry in the visible range. Laser Doppler flux was found to be generally higher around ulcers (mean = 4·7 ± 2·7 V) than in the dorsum of the foot of the same limb (2·3 ± 1·5 V), or in comparable sites (calf skin) of 20 control subjects (1·2 ± 0·4 V). Similarly, haemoglobin saturation was raised (46 ± 7 per cent), in comparison with values in dorsal and control skin (31 ± 13 per cent in both cases). In contrast, measurements of transcutaneous oxygen tension ($tcpO_2$) were lower around ulcers (22 ± 26 mmHg) than in dorsal or control skin (46 ± 33 mmHg and 70 ± 12 mmHg respectively), and in some cases very low indeed (<10 mmHg).

These observations are similar to results obtained in forearm skin using the tuberculin reaction as a model of chronic inflammation (Harrison *et al.*, Clin Phys Physiol Meas 13: 349, 1992). In this situation a barrier to oxygen diffusion, possibly presented by the infiltrating cells, has been suggested as a reason for poor oxygen transport between the well-perfused capillaries and the tissue cells, and consequently to the $tcpO_2$ electrode at the surface of the skin.

Statistical analysis was not appropriate in this current pilot study due to the relatively small numbers involved. Nevertheless, we believe that these results may indicate the existence of similarly impaired oxygen diffusion in ulceration. We plan to follow this work with a more extensive investigation of oxygen transport conditions in the microcirculation of leg ulcers.

Poster 024

Axillo-bipopliteal bypass graft: a report of 14 cases

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A group of patients has been identified in whom the presence of occlusive aorto-iliac disease is combined with occlusive femoral artery disease with disease in the profunda femoris artery but, nevertheless, a patent distal popliteal artery with an acceptable run off into the lower leg. The bipopliteal procedure was developed after a successful axillo-monopopliteal graft remained patent for four years. These patients with late-stage atheroma disease have all had severe intercurrent disease and limited life expectation and were not considered fit for an intra-abdominal operation. In this situation, the characteristics of the ring-reinforced Gortex graft material had been utilised to allow a long extra-anatomical bypass graft from the axillary artery to the distal popliteal artery, the graft being placed subcutaneously from the axilla across the costal margin over the musculature of the anterior abdominal wall placing the bifurcation so that a symmetrical acute angle bifurcation is formed in the flow-splitting pattern. The axillary component is an 8-mm-thin walled reinforced Gortex graft which exactly fits two 6-mm-thin walled ring Gortex grafts allowing a carina of 7·5 mm that is formed with 7/0 Prolene suture. The limbs of the graft cross the inguinal ligament and pass through the heads of the gastrocnemius muscle in the popliteal fossa to form an end to side anastomosis with the distal popliteal artery.

The bipopliteal procedure was developed after a successful axillo-monopopliteal graft remained patent for four years. The patients were selected as unfit for major abdominal surgery. Operative mortality was one from a myocardial infarct. Six died within one year although three thrombosed one limb of the graft when terminal illness caused hypotension. In the surviving seven patients, the patency has reached three years in four and the grafts are patent in the rest. No patient has required an amputation and the procedure has achieved successful limb salvage in all. These results are compatible with the small number of patients reported in the world literature and the procedure is a valuable means of achieving limb salvage in this, otherwise problematic, group of patients.

Poster 025

A new graft design to inhibit MIH at small-vessel anastomoses

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Autologous vein is the preferred material for infra-inguinal bypass grafting. In the absence of a suitable vein, bypass with PTFE may be the only alternative to amputation. One of the main causes of failure of these prosthetic grafts is the development of myointimal hyperplasia (MIH) at the distal anastomosis. Clinical evidence suggests that the effects of MIH may be reduced and patency rates improved by the interposition of a cuff of autologous vein between the graft and the recipient artery.

The mechanisms involved are not fully understood, but ongoing experimental work in our laboratory indicates that the cuff geometry may play a crucial role in inhibiting MIH. In cuffed anastomoses, we have found that high shear stress is maintained throughout the cardiac cycle by the presence of an organized vortex that occupies most of the cuff region.

We have investigated PTFE grafts with a cuff-like widening at the distal end which is created by balloon dilatation. Laboratory studies have shown flow patterns comparable to those observed in conventional vein cuffs. We implanted the new design grafts in patients with no adverse effects observed so far. Duplex scanning and DSA imaging demonstrate local haemodynamics similar to those of cuffed anastomoses.

Poster 026

Is carotid endarterectomy an under-utilised tool for stroke prevention?

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Carotid endarterectomy (CEA) reduces the risk of stroke or death in symptomatic patients with a >70 per cent internal carotid artery stenosis. The vascular surgeons of the USA perform 360 CEAs/million population. The UK rate has been between 24 and 32/million population. There is little evidence that the prevalence of carotid atherosclerosis is different between these populations. The aim of this study was to analyse trends for CEA in the UK between 1990 and 1993, and compare this with epidemiological and North American data.

The number of CEAs performed in the years 1990–93 for the English Health Regions and Scottish Health Boards were supplied by the Department of Health, England and the Information & Statistics Division of the National Health Service, Scotland respectively. Epidemiological data suggests that 160 people/million population have significant carotid arterial disease that warrants intervention. This estimate allows prediction of the number of CEAs that might be required for a population.

		No. CEAs performed					
Region	Population (million)	1990–91	1991–92	1992–93		Predicted CEAs	CEAs at USA rate
England	45	584	1288	1563		7200	16 200
CEAs/million		13	28	35			
		1990	1991	1992	1993		
Scotland	5·1	72	143	285	323	816	1850
CEAs/million		14·2	28·2	56·1	63·4		

ANOVA of regression over time: England: F Stat = 22·7, $P < 0·1$, Scotland: F Stat = 43·5, $P < 0·05$.

The rate of CEA in England and Scotland is increasing. Disease prevalence suggests that we should continue to increase the number of CEAs performed to optimise CEA as a method of stroke prevention, and may need to do so 3–6 fold. This would still mean that the UK was performing half the number of CEAs that occur in the USA. The implications to health care provision in the UK are wide ranging.

Poster 027

Follow-up of patients with small abdominal aortic aneurysms

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Many reports of management of aortic aneurysm concentrate on outcome after surgery. We have reviewed the outcome of patients with aortic aneurysm who have been placed in an ultrasound follow-up programme. All patients who had more than one ultrasound scan under the care of the vascular surgeons between 1988 and 1994 were identified from the radiology computer. There were 103 male and 31 female patients. The mean age at entry to follow-up was 70 years and the mean size of aneurysm at index scan 3·8 cm. Mean follow-up was 28 months and patients had a mean of 5 scans in this time. Sixty-five patients were referred by their GP (49 per cent), 20 by a urologist (15 per cent), 26 by a surgeon (19 per cent) and 15 by a physician (11 per cent).

Forty-five patients underwent surgery with 5 postoperative deaths (11 per cent). A further 3 patients died at 3 months, 2 years and 4 years postoperatively. Eighty-nine patients did not undergo surgery, with 18 deaths (20 per cent): 4 cardiac, 3 bronchial carcioma, 1 anaplastic carcinoma, 3 CVA, 3 pneumonia, 1 ruptured aneurysm, 1 renal failure from aortic thrombus, 2 unknown causes. Mortality in patients with small aortic aneurysms was 20 per cent when managed non-operatively, largely from causes other than aneurysm rupture. While low postoperative mortality may be reported, an overview of outcome in all patients with aortic aneurysm is useful.

Poster 028

Does angioplasty improve the quality of life in claudicants?

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Introduction and aims: Percutaneous transluminal angioplasty (PTA) is a commonly used intervention for claudication but it is not known whether PTA improves patients' quality of life (QOL) or if these potential improvements in QOL mirror changes in clinical indicators of lower limb ischaemia.
Patients and methods: Thirty claudicants (12 women and 18 men), median age 66 yr (range 42–82 yr) underwent 37 PTAs, 19 supra and 18 infra inguinal. Patients underwent measurement of ankle brachial pressure indices (ABPI) and maximum treadmill walking distance (MTWD) before completing the Short Form 36 (SF36) and EuroQol (EQ) questionnaires at interview 1 day prior to, and 1 and 3 months post PTA.
Results: Statistical analysis using Kruskal-Wallis Anova showed a significant improvement in ABPI and MTWD and SF36 domains of physical functioning, physical role, pain, vitality and social functioning ($P < 0{\cdot}01$). Using Spearman Rank Correlation there was a significant association between the EQ measured QOL and the (a) ABPI $r_s = 0{\cdot}51$, $P = <0{\cdot}01$ and (b) MTWD $r_s = 0{\cdot}6$, $P = <0{\cdot}01$.
Conclusion: PTA improves SF36 measured QOL domains. However at 3 months there was a downward trend in several QOL domains which did not reach statistical significance. This deserves further study. QOL as measured by the Euroqol correlates fairly closely with the clinical indicators of lower limb ischaemia and is also responsive to changes in disease severity and can be used as a reliable clinical outcome measure.

Poster 029

Suprarenal and high-risk aortic aneurysms by retroperitoneal approach

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The transperitoneal approach with inlay graft is now the accepted and most widely applied surgical approach to the infrarenal abdominal aorta. However, it is apparent that a significant proportion of aneurysms involve the thoracic and visceral portions of the aorta. With increasingly sophisticated imaging techniques available nowadays these aneurysms can be delineated preoperatively and any changes in operative technique instigated. The retroperitoneal approach to the abdominal aorta has been shown to reduce operative blood loss, postoperative ileus and hospital inpatient stay. Over the previous three years patients with suprarenal or high-risk abdominal aortic aneurysms (AAA) have been selected for this operative approach.

Fourteen patients underwent repair of the AAA by the retroperitoneal approach. Mean age (range) was 69 (58–77) years, with 10 males and 4 females.

Indications for surgery:

Aneurysm type	Number
Suprarenal	12
High risk	2

Four patients died within 30 days of operation due to myocardial infarction (2), internal iliac artery occlusion (1) and bleeding coagulopathy whilst on haemofiltration (1). Our early experiences suggests that for suprarenal and high-risk abdominal aortic aneurysms, the retroperitoneal approach provides excellent access and offers several advantages over the transperitoneal technique with an acceptable mortality.

Poster 030

What is the price of not having guidelines for the management of venous ulcers?

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The Wirral has been selected to be the National Pilot Site for implementation of draft national guidelines on the management of venous ulcers. Before introducing these, a comprehensive 12-week audit of current management by all health care workers has been carried out. Three hundred and nine patients with 350 ulcers were being treated (point prevalence 0·88/1000 population). The mean age was 79 years, the mean duration of current ulceration was 12 months. Thirty-seven per cent of ulcers were larger than 10 cm and 21 per cent were bilateral.

The mean time spent dressing an ulcer was 64 minutes per patient per week excluding the nurses' travel time, with 53 per cent of patients being treated more than once a week and 11 per cent treated 4 or more times per week. Despite this, 50 per cent were not given a new bandage every week. A total of 39 different preparations were put on the 350 ulcers and 29 different types of bandages applied over them in a wide variety of combinations. The cost of the items applied to the legs was a mean of £8.47 per ulcer per week. The healing rate over 12 weeks was 24 per cent. The annual cost of disposables was £154 154 and the cost of nurses' time to do the dressings was £194 133.

If the same patients were treated weekly with a four-layer bandage as proposed in the draft guidelines, this would cost two-thirds of current expenditure (£100 100) on disposables and lead to a saving in nursing time and an expected increased in healing rate, to about 68 per cent. Can we afford not to introduce guidelines?

Poster 031

The haemodynamic effect of sapheno-femoral/popliteal disconnection in patients with venous ulceration

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Elderly patients with venous ulceration may be best served by local anaesthetic interventions. We therefore examined the effects of local anaesthetic sapheno-femoral/popliteal disconnection on ambulatory venous pressure (AVP) measurements in 20 limbs. Fourteen limbs had superficial reflux only, 6 had combined deep and superficial reflux as defined by Duplex scanning.

The AVP allows calculation of the pressure relief index (PRI) [the product of the drop in venous pressure with exercise and time of venous refilling to 90 per cent of the resting pressure (RT90)].

The PRI of limbs with superficial reflux only, improved from a median (interquartile range) of 88 (27–178) preop to 273 (77–552) postop ($P = 0{\cdot}005$), that of patients with combined deep and superficial reflux was unchanged; 36 (4·6–131) preop and 32 (2·9–83) postop. The RT90 lengthened in those with superficial reflux only from 2·5 (1·25–4·7) s preop to 7·9 (2·75–10·9) s postop ($P = 0{\cdot}004$), whereas in the combined group, the RT90 remained unchanged 1·0 (0·4–3·1) s preop vs 1·2 (0·2–2·25) s postop.

In conclusion, local anaesthetic sapheno-femoral/popliteal disconnection improved venous haemodynamics in limbs with isolated superficial reflux, but had little effect on limbs with combined deep and superficial reflux – an important finding when considering venous surgery for ulceration.

Poster 032

Glutaraldehyde-tanned bovine carotid artery grafts for infra-inuginal reconstruction: 5-year follow-up

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Patency rates for vein grafts are superior to most artificial grafts, especially when examined over a long period. The St Jude graft is a glutaraldehyde-tanned bovine carotid artery product which theoretically confers improved long-term patency.

Sixty patients underwent placement of glutaraldehyde-tanned bovine carotid artery graft (BioPolyMeric, St Jude Medical Inc.) for severe peripheral vascular disease. Graft patency was assessed at yearly intervals with ankle Doppler measurement. Life-table and log-rank analysis were used to determine long-term cumulative graft patencies.

Cumulative patency was 80 per cent, 75 per cent and 70 per cent at 1, 3 and 5 years respectively. Six grafts were occluded within 30 days of surgery. Of the 16 blocked grafts observed, 3 patients required a major amputation, 2 below knee and one above knee. There were no graft aneurysms and no deep graft infections. Follow-up was for a minimum of five years.

St Jude grafts achieved patencies similar to those of vein grafts for femoro-popliteal bypasses, with an above knee distal anastomosis, at five years. Modified biological conduits offer a reasonable alternative to synthetic grafts for infra-inguinal arterial reconstruction and appear to maintain acceptable long-term patency rates when the autologous saphenous vein is absent or of inadequate size.

Poster 033

Profunda femoris revascularisation in critical limb ischaemia

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The value of isolated profunda revascularisation is often overlooked in the management of the critically ischaemic limb. Revascularisations to the isolated profunda femoris artery without any superficial femoral flow have been evaluated in 59 critically ischaemic limbs in 47 patients. The origin of the grafts was the aorta in 9 limbs, common iliac in 4, contralateral external iliac in 2, contralateral common femoral in 8, and an axillary artery in 32, together with 4 profundaplasties.

The mean follow-up was 747 (range 91–1670) days. Two limbs required an extension graft at 58 days and 413 days. One graft required a thrombectomy and one graft a revision in the immediate postoperative period.

There were 8 perioperative deaths, the cumulative patient survival being 83 per cent at 30 days, 72 per cent at 100 days, 66 per cent at 300 days, 59 per cent at 500 days and 37 per cent at 1000 days. Five limbs ultimately came to amputation, one below-knee after 497 days and four above-knee after 21, 473, 600 and 608 days, respectively. The cumulative limb salvage was 96 per cent at 30, 100 and 300 days, 87 per cent at 500 days and 76 per cent at 1000 days.

Isolated profunda revascularisation has been shown to be an effective method of limb salvage for the critically ischaemic limb.

Poster 034

Realistic expectations for limb salvage using the Miller cuff with infrageniculate bypasses – a prospective study

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In many patients with critical limb ischaemia there is no suitable autogenous conduit available for infrageniculate bypass. Synthetic grafts have reasonable patency rates above the knee, but when these conduits are used as bypasses to the infrageniculate arteries long-term patency and limb salvage are poor. Recent reports of infrageniculate bypass using a vein cuff or hood at the distral anastomosis have been more encouraging.

The results of 57 consecutive bypasses, in patients with critical limb ischaemia, to infrageniculate vessels using the Miller cuff at the distal anastomosis are reported. The mean age was 73 years (range 53–94) and the male : female ratio 28:29. There were 17 diabetics. The distal anastomosis was to the below knee popliteal artery in 23, and to the tibial vessels in 34 patients. Eighteen of the 57 patients had a previous failed bypass.

There were 2 perioperative deaths, both from cardiorespiratory complications. Life-table analysis of the primary (and secondary) patency rates at 30 days, 6 months, 1 year and 3 years was 86 per cent (88 per cent), 67 per cent (69 per cent), 62 per cent (64 per cent), and 51 per cent (54 per cent), respectively. Corresponding limb salvage rates were 89 per cent, 83 per cent, 77 per cent and 65 per cent respectively.

The results suggest that bypass using polytetrafluoroethylene with a Miller cuff to infrageniculate vessels is a worthwhile procedure, with acceptable patency and limb salvage rates when an autogenous conduit is not available in patients facing a major amputation.

Poster 035

Vasodilator responses or saphenous vein in diabetes: implications for bypass graft patency

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There has been a prejudice that diabetes modulates the function of saphenous vein in a manner that predisposes to bypass graft failure, although most of the evidence accrues from animal studies. We have investigated the effects of diabetes on the vasodilator responses on saphenous vein harvested from patients undergoing bypass surgery.

Endothelium-derived relaxing factor (NO) production stimulated by receptor-activated pathways (bradykinin and thrombin) was not different in rings from diabetics ($n = 12$) and non-diabetics ($n = 12$). Endothelium-independent relaxation in response to sodium nitroprusside was not different in rings from diabetics and non-diabetics. The synthesis of prostacyclin, measured as 6-keto $\text{PGF}_{1\alpha}$, was 112·2 ± 20·4 pg/cm^2/min in non-diabetics and 65·9 ± 27·0 pg/cm^2/min in diabetics, $P = 0{\cdot}011$. Endothelium-dependent relaxation to fibrinogen (2 μM), effected by a K ion channel pathway, was 61 ± 5 per cent in non-diabetics compared with 8 ± 5 per cent in diabetics.

Since our clinical studies have shown that fibrinogen, but not diabetes, is a risk factor for vein graft stenosis and occlusion, the current results support three hypotheses concerning vasodilator responses and vein graft patency: NO production (normal in diabetics) is critical, prostacyclin production (reduced in diabetics) is of minor importance, and inhibition of the fibrinogen response (as in diabetics) may be beneficial. Saphenous vein should continue to be used for bypass surgery in diabetics.

Poster 036

Leucocyte CD11B/CD62L activity in patients with venous disease

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Leucocyte trapping in the microcirculation of the leg has been reported in patients with venous disease. We investigated this activity further by measuring the integrin CD11b and selectin CD62L on both neutrophils and monocytes in 20 patients with venous disease. Blood samples were taken from a foot vein after lying supine for 20 minutes, standing supported for 30 minutes, and after lying supine again for 10 minutes. The samples were analysed for full blood count, and CD11b and CD62L were measured by a whole-blood assay using fluorescent monoclonal antibodies in a flow cytometer.

	Group I (skin change present, $n = 9$)				Group II (skin change absent, $n = 11$)			
	Neutrophils		Monocytes		Neutrophils		Monocytes	
	CD11b	CD62L	CD11b	CD62L	CD11b	CD62L	CD11b	CD62L
Basal	4·48*	5·06*	7·88*‡	2·44*	4·67*	6·27*	6·51*	3·41*
Standing	3·65*†	4·82*†	5·61*†	2·3*†	3·85*†	5·5*†	4·95*†	3·14*†
Supine	3·34†	4·57†	5·43†‡	2·07†	3·48†	6·04†	4·4†	2·85†
Wilcoxon	* = 0·03	* = ns	*† = ns	* = 0·05	* = 0·003	* = 0·04	* = 0·003	* = 0·01
$P =$	† = ns	† = 0·02	‡ = 0·015	† = ns	† = 0·02	† = ns	† = ns	† = 0·004

There was significant leucocyte trapping as shown by a fall in the WBC:RBC ratio after standing (median 1·33 to 1·31, P = 0·026, Wilcoxon) followed by a rise after returning to the supine position (median 1·43, P = 0·0002). In both groups of patients CD11b and CD62L levels on neutrophils and monocytes fell following venous hypertension, and this fall was sustained even after assuming the supine position. There was no significant difference between the two groups. This finding is in contrast to that in normal volunteers in whom a rise in the CD11b expression was previously noted in samples collected 10 minutes after assuming the supine position following venous hypertension.

This suggests that leucoycte-endothelial adhesion is more exaggerated in patients with venous disease compared to normal volunteers.

Upper Gastrointestinal

Poster 037

Changes in the lymphocyte subsets of regional lymph nodes in patients with gastric cancer

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Regional lymph nodes (RLN) are believed to act as a first line of defence against the spread of gastric cancer (GC) and their importance is underlined by the impressive results achieved by D2 gastrectomy with radical lymph node clearance. Whilst there are many studies documenting changes in immune function in the peripheral blood of patients with GC, little is known about what changes occur in RLN. The aim of this study was to measure the lymphocyte subsets in the RLN and peripheral blood of patients with GC.

Lymph nodes from 17 patients with adenocarcinoma of the stomach were harvested in theatre in the course of radical (D2) gastrectomy. Lymphocytes were extracted from the lymph node by flushing with RPMI solution. Monoclonal antibodies were then used to determine the lymphocyte subsets of both the RLN and peripheral blood. Results are expressed as the percentage of lymphocytes expressing a particular antigen.

Results:

	CD3	CD4	CD8	CD19	CD16
Peripheral blood	67	45	16	13*	15**
Metastatic nodes	68	46	11	33*	0·5**
Uninvoled nodes	65	49	12	32	0·5

*$P < 0·001$, **$P < 0·001$.

There were significantly fewer natural killer cells (CD16) but considerably more B-cells (CD19) in RLN compared with that of the peripheral blood. The alteration of lymphocyte expression in the RLN may be an important factor in the rapid spread of gastric cancer via the lymphatic system.

Poster 038

Histological cellular effects on gastric mucosa following vagotomy

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Experimental gastric serosal defocused carbon dioxide laser irradiation results in a significant reduction of pentagastrin-stimulated acid output as well as a reduction in cysteamine-induced peptic ulceration. This study assessed histological mucosal sub-population following conventional highly selective vagotomy and defocused carbon dioxide laser irradiation.

Ninety male Sprague-Dawley rats were randomised to three groups: control, surgical highly selective vagotomy (HSV) and defocused serosal irradiation with the carbon dioxide laser (laser-S). Maximal pentagastrin-stimulated acid output and serum gastrin levels were analysed to confirm a vagotomy effect. Histological analysis of mucosal sub-population of cell types (cells per crypt), as well as vagal cell density (number of cells per high-power field) on the serosal surface were determined. Results were:

Group (n = 30)	Vagal	Parietal	Oxyntic	Mucous
Control	6·8	29·4	15·5	12·9
Surgical-HSV	1·2*	27·4	16·6	11·0
Laser-S	1·7*	30·7	12·4	12·1

*$P < 0·05$ vs Control.

The results show a significant reduction in the vagal density following vagotomy; however, there are no significant changes in the gastric mucosal sub-population following either conventional highly selective vagotomy or carbon dioxide laser irradiation to gastric serosa.

Poster 039

An assessment of intraluminal microselectron and external beam radiotherapy in the treatment of oesophageal carcinoma

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A large number of patients presenting with oesophageal carcinoma are elderly with significant co-morbid conditions, present with advanced disease and are unfit for surgery. Radiotherapy offers palliation for many of these patients and may be delivered by external beam (EBR) or intraluminally. Intraluminal radiotherapy delivers a high dose locally to the tumour while sparing adjacent normal tissue. Conventional intraluminal selectron therapy necessitates prolonged sedation while microselectron is delivered over a shorter period of time. The aim of this prospective study was to examine outcome and survival following combined treatment with EBR and microselectron in patients presenting with oesophageal carcinoma who were unsuitable for surgery. A total of 85 patients underwent treatment following the introduction of microselectron in 1993. The mean (SEM) age of patients was 72·5 (0·9) years and 35 were female. A median dose of 30 cGy was delivered by EBR and 10 cGy was delivered intraluminally over a mean (SEM) of 9·5 (0·5) minutes. There were no deaths as a result of microselectron; one patient suffered an aspiration pneumonia which settled on antibiotics. Dysphagia scores improved significantly following the procedure from a mean (SEM) of 1·5 (0·1) to 1·2 (0·2) (P < 0·05). The median survival following microselectron was 22 weeks (95 per cent confidence intervals 18·1–25·9 weeks). Survival was dependent on length of the tumour (≤3 cm – 47 vs ≥ 4 cm – 21 weeks; P < 0·01), the presence of coeliac lymph nodes (present – 19 vs absent 34 weeks; P < 0·05) and the presence of metastases (present – 16 vs absent – 26 weeks; P < 0·05). Patients with squamous cell carcinoma survived longer than those with adenocarcinomas but the difference was not significant. Survival was not dependent on the grade of tumour, the sex of the patient or the level of the tumour. This technique of high-dose remote afterloading is well-tolerated by the patient, and is associated with a low morbidity and an acceptable survival in combination with external beam radiotherapy.

Poster 040

Use of expandable stents in the treatment of oesophageal carcinoma and tracheo-oesophageal fistula

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Palliation for malignant dysphagia has relied on oesophageal dilatation, insertion of rigid prostheses and laser treatment. All three methods carry a substantial risk of perforation. Displacement of the tube is also well described.

Fourteen expandable polythene-covered metal stents were inserted in twelve patients with oesophageal carcinoma (median age 70 years). Eleven were inserted for dysphagia and three for tracheo-oesophageal fistulas (TOFs). Stents were inserted endoscopically under fluoroscopic control. Median dysphagia scores before and after insertion were 3 (range 2–4) and 1 (range 1–2) respectively. Stent insertion provided cure of symptoms in both patients with TOFs. Median postoperative hospital stay was one night (range 0–4) following insertion. There were no deaths and no perforations associated with the procedure. Two patients complained of retrosternal chest pain for 2 days following the procedure but there were no other complications associated with insertion. Another patient developed a TOF following radiotherapy four months after stent insertion. A second stent was inserted with successful control of symptoms. This man developed a second TOF and has had a third stent successfully inserted. Two patients died 1 month and 6 months after stent insertion. Median follow-up of the remainder is 2 months (range 1–9 months) during which time there has been no deterioration in symptoms of dysphagia.

Expandable oesophageal stents offer a safe alternative to traditional methods of palliative treatment for oesophageal carcinoma. In the long-term they may provide a cost-effective alternative to laser treatment.

Poster 041

Early oesophagectomy is associated with improved survival in perforated oesophageal carcinoma

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For patients with iatrogenic perforation of oesophageal carcinoma the timing and type of surgery remain controversial. A case note review identified 18 patients in the 10 years to December 1992 who had carcinoma of the oesophagus and underwent oesophagectomy after instrumental perforation.

Oesophagectomy was performed within 48 hours of perforation in 10 patients (early surgery group) and after a median delay of 22 days (range 5–48 days) in 8 patients (delayed surgery group). All patients underwent resection via a left thoracolaparotomy with immediate intrathoracic anastomosis, using the stomach in 17 of 18 patients. There were no anastomotic leaks. For the early surgery group, mean operative blood loss was 410 ml, postoperative complications occurred in 5 of 10 patients with 2 in-hospital deaths and the mean survival was 551 days (range 17–1780 days). In the delayed group, mean operative blood loss was 1088 ml, 6 of 8 developed postoperative complications with 2 in-hospital deaths and mean survival was 297 days (range 21–546 days).

Transthoracic resection with immediate anastomosis can be performed without anastomotic leakage despite a high (predominantly respiratory) postoperative morbidity and 22 per cent mortality. Early oesophagectomy has little effect on hospital morbidity or mortality but may result in better use of resources and improved long-term survival.

Poster 042

The effects of neoadjuvant chemoradiotherapy and surgery on the immune system of patients with carcinoma of the oesophagus

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The aim of this study was to quantify the response of the immune system to neoadjuvant chemoradiation followed by resection in patients with oesophageal cancer.

Lymphocyte subsets and natural killer cell function were measured in 12 patients (M:F 6:6, median age 62 yr) with oesophageal carcinoma who received multimodality treatment, and were compared with the results of controls who underwent surgery alone. Chemotherapy consisted of two courses of fluorouracil 1 g/m^2 for 4 days and cisplatin 80 mg/m^2 on day 1. Six patients also received radiotherapy (20 Gy in 5 fractions). All patients underwent oesophagogastrectomy 4 weeks later. Cell-mediated immunity was measured before (pre-R$_x$) and after (preop) chemoradiation and on days 7, 14 and 84 after operation. NK cell cytotoxicity was determined by a Cr^{51} release assay.

Results: (NK cell per cent lysis)

	Pre-R$_x$	Preop	Day 14	Day 84
Chemoradiation + surgery	27 per cent	13 per cent*	16 per cent*	12 per cent*
Surgery alone	—	28 per cent*	28 per cent*	23 per cent*

*$P < 0{\cdot}05$

Cell-mediated immunity was significantly depressed after chemoradiation. Radical surgery did not result in further immunosuppression, but recovery of cell-mediated immunity was delayed in the treatment group and was still significantly depressed 3 months after operation.

Poster 043

Are preoperative respiratory function tests a useful predictor of pulmonary complications in patients after surgery for gastric cancer?

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Despite recent advances in surgical technique and anaesthetic management, respiratory complications are still a major cause of morbidity and mortality in patients who undergo surgery for gastric cancer. Whether preoperative respiratory function tests are of value in identifying patients at risk of pulmonry complications remains unclear.

We reviewed the respiratory function tests and ASA scores in 108 patients (male:female 70:38, median age 70 years) who underwent surgery for gastric cancer. Patients were divided into two groups using the following well-recognised criteria: forced vital capacity (FVC) less than 75 per cent of predicted value, forced expiratory volume in 1 second (FEV$_1$)/FVC ratio less than 65 per cent, and ASA score greater than 2. The incidence of postoperative respiratory complications was recorded for each group.

Results	FVC <75 per cent	FVC >75 per cent	FEV$_1$/FVC <65 per cent	FEV$_1$/FVC >65 per cent	ASA > 2	ASA ≤ 3
Respiratory complications (per cent)	25	21	41**	16**	36*	15*
No respiratory complications (per cent)	75	79	59	84	64	85

*$P < 0{\cdot}05$, **$P < 0{\cdot}02$.

Patients with a FEV_1/FVC ratio of less than 65 per cent and those with an ASA grade of greater than 2 were found to be at higher risk of developing respiratory complications after operation, and may possibly benefit from bronchodilators and vigorous physiotherapy before and after surgery.

Poster 044

Upper gastrointestinal microbial flora and postoperative respiratory infection

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Postoperative respiratory infection (PORI) is a common problem following major oesophagogastric resections. There has been no progress in reducing the incidence in the last 25 years.

We have performed a prospective study of the microbial flora in the oropharynx preoperatively and in the oesophagus at the time of oesophagogastrectomy. Thirty patients were studied. Sixteen (53 per cent) developed PORI. Three had positive preoperative throat swabs and two developed PORI with the same organism. The third, who had significant chronic airways disease, was given antibiotics to cover the operation and made an uneventful recovery. Six patients had significant growth from the oesophageal contents obtained at the time of operation. All developed PORI, but this involved the same organism in only two patients. Throat swabs obtained at the end of the operation were uniformly negative.

These investigations identified eight of the 16 patients who developed PORI. Monocolonisation of the upper gastrointestinal tract appears to be a significant marker for subsequent infection, but not necessarily with the same organism. There are interesting differences between the significance of pharyngeal and oesophageal pathogenic organisms.

We believe that these data provide some basis for more detailed study of strategies to reduce the impact of PORI.

Hepatobiliary/Pancreatic

Poster 045

Evolving management of common bile duct stones

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Over a five-year period 173 patients presented with CBD stones. One hundred and five patients were treated by ERCP and 85 (81 per cent) were successful. Of the 20 patients with retained stones, 18 underwent surgical exploration, and 2 patients were treated conservatively.

Sixty-eight patients underwent primary surgery. Of these, 54 had open exploration of the CBD and 47 (87 per cent) were successful. Eighteen patients underwent primary laparoscopic exploration (4 cases were converted). Of the 14 completed, 12 (86 per cent) were successful. Thus a total of 9 (13 per cent) patients had failed primary surgery and were treated as follows: ERCP (n = 7), dissolution therapy (n = 1), conservative treatment (n = 1). There was no mortality in the entire series. The complication rate with ERCP was 12·4 per cent and included pancreatitis (8 per cent), cholangitis (2 per cent), haemorrhage (2 per cent) and obstruction (1 per cent). With open surgery the complication rate was 13 per cent and included wound infection (7 per cent), DVT (2 per cent), pneumonia (2 per cent) and bile leak (2 per cent). Of the 14 patients undergoing laparoscopic exploration, there were no complications. There was no significant difference in hospital stay between the three groups. All patients are well on follow-up.

The management of choledocholithiasis is in evolution, and laparoscopic CBD exploration is an additional treatment option.

Poster 046

Symptoms of oesophageal reflux are more common following laparoscopic cholecystectomy

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Previous studies have shown that 40 per cent of patients have symptoms after cholecystectomy or laparoscopic cholecystectomy (LC). Abdominal symptoms in 212 patients following LC were compared to a healthy acalculous (by ultrasound) control population (n = 62). Patients and controls were assessed by questionnaire.

Age and sex profiles were similar in both groups. There was no significant difference in the incidence of abdominal pain, bloating or nausea between the two groups; 19·3 per cent of patients complained of frequent heartburn following LC as compared to 3 per cent of control patients ($P = 0·05$). Furthermore 11·3 per cent of postoperative patients complained of dysphagia versus 6 per cent of the control group ($P < 0·05$). One hundred and twenty (57·1 per cent) patients judged their operation to be a success, while 9 (4·3 per cent) were dissatisfied.

Abdominal pain, bloating and nausea occur as frequently in the general population as in patients following LC. Patients are more likely to suffer from heartburn and dysphagia following LC than a normal population, suggesting a link between cholecystectomy and lower oesophageal dysfunction.

Poster 047

The assessment of risk factors for common bile duct stones

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One of the dilemmas facing clinicians in the management of common bile duct stones is that in only 20–60 per cent of patients undergoing preoperative endoscopic retrograde cholangiopancreatography (ERCP) are stones actually identified. A study has been performed aimed at reassessing the criteria for ERCP in these patients.

Two groups of patients were assessed: 156 patients who had undergone laparoscopic cholecystectomy with successful operative cholangiography clearly demonstrating the absence of common bile duct stones. The study group comprised 77 patients who had clearly demonstrated common bile duct stones at ERCP. Clinical, biochemical and ultrasound abnormalities were documented and a multivariate analysis was performed.

The results identified jaundice, ascending cholangitis, alkaline phosphatase, transaminases, common bile duct dilatation or stone on ultrasound as being significant at predicting the presence of common bile duct stones. Using these, with each factor weighted according to its relative significance, a scoring system was devised. The range was 0–16; if the score is 0–2 the patient need not undergo ERCP. The sensitivity of the scoring system in this group was 84 per cent, the specificity was 94 per cent.

The use of this scoring system should lead to a reduction in the number of unnecessary ERCPs. It is currently being tested prospectively.

Poster 048

Laparoscopic cholangiography – X-ray or image intensifier?

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We performed a prospective randomised study comparing the portable C-arm image intensifier (II) and the standard X-ray machine during laparoscopic cholangiography (LC). Cholangiography technique was standardised and a selective preoperative ERCP policy employed. The cholangiogram quality, the time taken to perform the procedure, the success rate and a subjective evaluation of the difficulty of the procedure were assessed. The distance between the clip holding the cholangiogram catheter in the cystic duct and the common duct was measured and called the 'critical length'.

One hundred and ninety-seven patients were studied and LC was attempted in 186 and was successful in 93 per cent. In 15·6 per cent of X-ray cholangiography, more than the standard 2 films were required. The critical length was ≤1 cm in 1/3 of patients but did not affect the conversion rate which was 10·2 per cent. The mean LC time (mins) for II was 15 (7–30) and for X-ray was 23 (10–50) ($P < 0{\cdot}0001$). The overall operation time was not significantly affected. The procedure was considered 'easy' in 59 per cent of cases. The surgeon considered 90 per cent of II and 86 per cent of X-ray images satisfactory compared to just over 80 per cent (II and X-ray) by the radiologist.

Critical length assessment may avert diathermy or clip injury of the common duct. The II offers greater versatility and the ability to obtain more rapid and complete radiology.

Poster 049

Referral patterns of liver metastases in colorectal cancer: too few, too late?

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It is estimated that 40 per cent of all patients with colorectal cancer will develop liver metastases and, if untreated, the median survival is approximately 6 months. Surgical resection is currently the only treatment with any prospect of cure. Despite increasing numbers of referrals for liver resection, there are many potentially curable patients who are dying of colorectal metastases (CRM). Estimates of resectability rates have been disappointing because many patients continue to present only when they become symptomatic.

Between 1986 and 1993, 43 hepatic resections were performed in this regional referral centre for CRM (region population 3·6 million; 1900 colorectal cancer cases/year). Only one could be dealt with by segmental resection. The other 42 tumours necessitated hemihepatectomy or extended hemihepatectomy procedures. Actuarial 5-year survival was calculated to be 39 per cent, but was 85 per cent for those patients in whom a greater than 1 cm clearance was achieved, versus 21 per cent for the remainder ($P < 0{\cdot}05$, log rank chi-square).

Our results suggest that patients with CRM are presenting for hepatic resection late in their disease, yet acceptable cure rates are being achieved. Earlier referral may improve the outcome of this difficult group.

Poster 050

Surgery for cystic disease of the liver

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During the past two years 18 patients have been referred to this regional hepatobiliary unit for consideration of surgery for cystic liver disease. It has been our policy to use CT or MRI to investigate any suspicious features on ultrasound. Diagnoses have been: polycystic liver disease (6), simple hepatic cyst (5), cystadenoma (3), cystadenocarcinoma (2), polycystic liver and kidney disease (2).

Surgical treatment has been carried out on the basis of symptoms of pain or distension and failure of aspiration therapy for simple/polycystic disease and for evidence of cystadenoma/carcinoma on imaging. One cystadenocarcinoma was inoperable, one was resected by right trisegmentectomy. The 3 cystadenomas underwent resection: 2 segmental, 1 right hepatectomy. Simple/polycystic disease has been dealt with by laparoscopic fenestration (4) or laparoscopic resection of the entire cyst wall (3). One case involved a formal laparoscopic left hepatectomy.

One cyst recurred following fenestration and was resected laparoscopically. One patient died from heart failure during right hepatectomy. There were no other complications. The two patients with polycystic liver and kidney disease are awaiting combined liver and kidney transplantation. Three patients with polycystic liver disease are being managed symptomatically.

Poster 051

Acute pancreatitis: 144 patients treated in a tertiary centre

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Between 1988 and 1995, 144 patients with acute pancreatitis were treated by one consultant (MJM). Of these, 70 were admitted from the local population and 74 were tertiary referrals. Mean age was 53 years (17–91) and 90 were men. The aetiology was alcoholic in 44, gallstones in 51, idiopathic in 33 and other causes in 16.

The ASA grades of the 144 patients were: ASA I 76, ASA II 33, ASA III 33 and ASA IV 2 patients. The mean APACHE II score on admission was 7·3 (range 0–35). Dynamic CT imaging was performed in 99 patients and formed the basis for all subsequent management. Thirty-four patients had one CT scan, 23 patients two scans, 11 patients three scans and 31 more than three scans.

Of the 144 patients, 74 were managed conservatively without operative or radiological intervention, 33 had radiological intervention and 33 required operation. Forty of the 144 cases required intensive care support and 79 needed intravenous nutrition. Twenty-seven of the 144 patients required open pancreatic debridement. Of these 27 patients 19 died but 8 survived. Overall 26 of the 144 (18 per cent) patients died from their pancreatitis. The best predictor of overall mortality was the APACHE II score on admission ($P < 0{\cdot}001$). Mean length of stay was 44 days (range 1–173) and for those requiring operative debridement, 52 days.

This group of patients poses a formidable challenge and places great demand upon the therapeutic and support services of the hospital. For severe acute pancreatitis the full range of therapeutic and support services should be available with management based upon clinical and radiological features and progress.

Poster 052

Percutaneous stenting for failed endoscopic stenting in distal biliary obstruction

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Endoscopic stenting is a satisfactory treatment for patients with distal biliary tract obstruction. However, for those in whom an endoscopic approach has failed, the optimum management has not been established.

Over a 3-year period, of 133 patients referred for percutaneous endoprosthesis insertion, 29 patients with distal biliary obstruction had previously failed an endoscopic attempt at stent placement (failed cannulation – 24, duodenal stenosis – 2, duodenal diverticulum – 2, previous gastric surgery – 1). All patients were jaundiced, whilst 20 (90 per cent) had pruritus and 9 (31 per cent) had abdominal pain. The aetiology was carcinoma of the pancreas (15), bile duct carcinoma (8), peri-ampullary carcinoma (3), nodal metastases (1), and benign stricture (2).

Percutaneous stenting succeeded in 25 patients (86 per cent). Of the 4 failures, 2 patients with advanced cancer died following the procedure. There was one in-hospital death (4 per cent) in the group successfully stented.

Five patients developed acute cholangitis which responded to antibiotics. Of the 26 patients discharged from hospital, 8 (31 per cent) were readmitted with stent blockage or cholangitis. These were successfully managed with stent change.

Percutaneous stent placement for distal biliary obstruction is successful and effective in patients failing an endoscopic approach.

Poster 053

Chemoembolisation for primary hepatocellular carcinoma

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Surgical resection is the only curative treatment for primary liver cancer. The median survival of patients with untreated hepatocellular carcinoma is one month from the time of diagnosis. Targeted arterial embolisation (TAE) of chemotherapeutic agents has been used in the palliation of unresectable lesions and rarely for marginally unresectable lesions prior to an attempt at resection. Between January 1989 and March 1995, 37 patients were treated with TAE, 2 prior to surgical resection and 3 for recurrence following previous resection. In the remaining 32 patients, TAE was the only treatment given. There were 26 men and 11 women with a mean age of 63 yr. The number of embolisations in each patient varied from 1 to 4 (a total of 62 procedures), the procedure being repeated if the response was found to be adequate. The median survival in this group was 166 days and the cumulative survival was 80 per cent at 3 months, 40 per cent at 6 months and 15 per cent at 9 months and 1 year. Of the 2 patients who had resection after embolisation, one died from recurrence after 795 days and the other patient is alive 686 days following resection. Targeted hepatic arterial embolisation provides worthwhile survival benefit in patients with unresectable hepatocellular carcinoma.

Poster 054

Lithium gamma linolenic acid in pancreatic cancer

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Lithium salt of gamma linolenic acid (LiGLA) has been reported to prolong the survival of patients with inoperable pancreatic cancer. We studied the effect of LiGLA on 2 pancreatic ductal cancer cell lines (Pancl and MIA PaCa2) *in vitro* and on MIA PaCa2-derived pancreatic tumour in athymic mice.

For *in vitro* study the cells were seeded at 2500 cells per well in 96-well culture plates. LiGLA (Scotia, Guildford, UK) was added 24 h later (5–490 µmol/l). A human fibroblast cell line was used as the control. Oleic acid (OA), palmitic acid (PA) and lithium chloride (LiCl) controls were used to exclude a non-specific fat overload effect and a lithium effect. The surviving fraction of cells after 7 days was assessed by the MTT assay. For *in vivo* studies, Balb c nude mice were inoculated subcutaneously over the right flank with 5×10^6 MIA PaCa2 cells. Once progressive tumour growth was confirmed they were treated with LiGLA IV over 10 days (total dose 0·8 mg/g body weight). The control group received lithium oleate. The tumour size was measured weekly for 4 weeks following therapy.

LiGLA showed a selective and significant dose- and time-dependent growth inhibitory effect on both cancer cell lines *in vitro* (IC$_{50}$ of MIA PaCa2 = 10·7 µmol/l, Pancl = 12·6 µmol/l). By contrast the IC$_{50}$ of fibroblasts was 110·8 µmol/l. OA, PA and LiCl had no effect. A significant reduction of tumour growth rate was achieved in mice with subcutaneous tumours that received LiGLA, compared with controls. LiGLA has none of the side-effects of conventional chemotherapy and may prove useful in pancreatic cancer.

Poster 055

Carcinoma of the gallbladder is rare, but beware!

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Interest in this rare carcinoma has been aroused with development of port site metastases in patients after laparoscopic cholecystectomy.

The notes of twelve patients with gallbladder carcinoma diagnosed between 1991 and 1995 were reviewed: five were incidental cancers found during cholecystectomy, five were symptomatic and two were incidental autopsy findings. In this period there were 1200 cholecystectomies, thus the incidence of carcinoma was 0·4 per cent. All the 'symptomatic' patients died of gallbladder carcinoma, with a mean survival of six months. The incidental cancer patients had a mean survival of 14 months. Of the three cholecystectomies attempted laparoscopically, one subsequently developed port site metastases within six weeks. Two patients had disease not breaching the serosal surface: one is alive at six months with no evidence of recurrence, and one patient died after eleven months of an unrelated cause with no evidence of recurrence of gallbladder carcinoma. All three patients with > stage III disease following cholecystectomy died, with a mean survival of seven months.

Conclusions:

1. The incidence of incidental gallbladder carcinoma was lower than previously reported.
2. None of the incidental cancers were suspected macroscopically.
3. Incidental cancer has a better prognosis than symptomatic cancer, particularly if it is < stage III.

Lower Gastrointestinal

Poster 056

Magnetic resonance imaging of anal sphincter sepsis using an internal coil – preliminary studies

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Magnetic resonance imaging (MRI) of perianal sepsis has variable accuracy due to its poor anal sphincter resolution leading to difficulty in localising abscesses, fistulous tracks and their internal openings. We have studied whether the MR images with an internal coil can improve preoperative evaluation of anal sepsis.

Ten patients with perianal sepsis, 7 men, median age 38 years (range 25–63 years), were studied. A cylindrical coil (diameter 9 mm, length 75 mm) was positioned endoanally and images acquired using T1 and T2 weighted and STIR images after contrast. The scans were evaluated preoperatively by 2 radiologists; the consensus view was compared with the independent surgical findings.

At surgery, all 10 patients had sphincteric abscesses of which 6 were intersphincteric, 2 ischiorectal and 2 mixed. Five patients had an associated fistula *in ano* (2 transphincteric, 3 intersphincteric); the internal opening was at the dentate line in 4 patients. There was concordance between MRI and surgery for location of abscesses in 100 per cent, site of the fistulous track in 80 per cent and for internal opening position in 80 per cent. At 6 months follow-up, all wounds had healed with no recrudescence of sepsis.

These data show that MR with internal coil improves accuracy in imaging perianal sepsis; confirmatory studies are in progress.

Poster 057

Continence following low anterior resection – neorectal dynamics and anal physiology

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A previously validated model for the assessment of rectal physiology based on accurate *in vivo* ultrasonic measurements and established physical principles[1] was used for the analysis of neorectal dynamics and continence following low anterior resection.

Twenty-four patients who had low anterior resection were recruited. Three groups were identified according to their functional score: major incontinence (score 4–7) ($n = 5$), minor incontinence (score 2–3) ($n = 8$), and normal continence ($n = 11$). These groups were comparable in terms of clinical and anastomotic characteristics and anal squeeze and resting pressure.

With an anastomosis at or below 7 cm from the anal verge, rapid inflation of the rectal balloon caused a sustained drop in anal pressure with no evidence of recovery. This prolonged anorectal inhibition was not seen with anastomoses above 7 cm. Major incontinence was associated with a high neorectal wall stiffness and disordered viscoelastic parameters with evidence of decreased elasticity within the neorectum. Strain work was increased at all rectal sensations. Sequential multivariate analysis of the models' parameters revealed the smooth muscle component to be significantly ($P = 0{\cdot}01$) increased.

This study demonstrates that major incontinence following low anterior resection is due to a prolonged rectoanal inhibitory reflex associated with increased neorectal wall stiffness caused by increased neorectal smooth muscle activity.

1. Pressure Modulus – A Challenge to the Concept of Compliance. Presented at the Surgical Research Society, Manchester 1995. Abstract Br J Surg 1995 (in press).

Poster 058

Enhanced MRI for the differentiation of local recurrence and scar following curative surgery for rectal cancer

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The differentiation of local recurrence from scar following resection of rectal cancer remains a problem. Malignant tissue has different paramagnetic contrast uptake characteristics on MRI than scar or normal tissue, showing greater and faster enhancement. We have analysed rate and magnitude of enhancement in patients with a suspicious pelvic mass and compared the results to tissue diagnosis from needle or open biopsy.

Seven rectal cancer patients with suspicious non-enhanced follow-up MR scans were studied. Dynamic contrast-enhanced MRI was performed and regions of interest were defined. A series of mean pixel values were obtained for each region. Regression techniques on the initial linear uptake region allowed calculation of a rate of uptake and identification of baseline and plateau values and allowed degree of enhancement (Contrast Enhancement Index, CEI) to be determined.

In all cases of recurrence (histologically confirmed), rate of enhancement was significantly greater than in scar tissue. There was overlap of CEI between recurrence and scar. One case showed overlap of rate between normal tissue and recurrence but separation on the basis of CEI. A scatter plot of rate of enhancement against CEI provides an absolute separation of points which seems diagnostic for recurrence. This is the first time that MRI has produced diagnostic accuracy to this degree.

Poster 059

Transanal stapled anastomosis following restorative resection for rectal cancer is associated with long-term injury to the internal anal sphincter

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Disorders of continence are present in up to half of all patients undergoing restorative resection for rectal cancer. Transanal stapling involves anal dilatation and may contribute to sphincter injury. We have prospectively assessed anal sphincter morphology in 39 patients [21 men; median age 59 (range 47–84) years] undergoing restorative resection for rectal cancer by means of endoanal ultrasound to assess whether such dilatation results in the disruption of anal sphincters.

Endoanal ultrasound was performed preoperatively, immediately after surgery, and at 4, 6 and 12 months post-surgery. The staple gun size used was 29 mm (27 patients), 31 mm (8 patients), and 28 mm (4 patients). The results are summarized in the following table:

	Preop	Immediate postop	4 months postop	6 months postop	12 months postop
Internal sphincter defect present	0/39	7/39	7/39	7/39	7/39
External sphincter defect present	3/39	2/39	2/39	2/39	2/39

Transanal stapling for the restorative resection of rectal cancer was associated with evidence of disrupted internal anal sphincter morphology in 18 per cent of patients studied. These defects persist one year after surgery. External anal sphincter morphology was not affected by the procedure.

Poster 060

Why do W reservoirs empty more efficiently than J reservoirs after restorative proctocolectomy (RP)?

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Pelvic ileal reservoir emptying was compared in 34 patients with either J or W pouches one year after RP for ulcerative colitis. A standard volume subtraction method was compared with direct gamma camera imaging.

In each patient, the ileal reservoir was filled with up to 600 ml of methyl cellulose paste labelled with ^{51}Cr-chromate and ^{99m}Tc-DTPA. Percentage evacuation was calculated from the difference in activity of ^{51}Cr between the original 600 ml of paste, the unused paste after pouch filling and the collected effluent, and compared with gamma camera measurements of ^{99m}Tc-DTPA activity within the ileal reservoir before and after evacuation.

	$n =$	Percentage evacuation		Volume
		^{51}Cr	Gamma camera	
J pouches	20	70 (65–76)*	70 (63–76)	423 (298–523) ml
W pouches	14	88 (77–94)*	85 (76–92)	308 (236–467) ml

Median (IQ range), * $P < 0{\cdot}01$.

Ileal reservoir emptying was inversely correlated to reservoir volume (Rs = $-0{\cdot}53$; $P = 0{\cdot}002$). W pouches appeared smaller and emptied more efficiently than J pouches.

Gamma camera measurement of ileal reservoir emptying is as accurate as our previous standard technique. In addition, the gamma camera provided a qualitative record of pouch evacuation, which may be of clinical value, and which revealed that the differences between J and W reservoirs may be due to reflux of paste into the afferent ileum occurring more frequently in J pouches than in W pouches.

Poster 061

Colorectal carcinoma: a regional audit of pathology reports

A.D. Bull, J. Mella, A. Biffin, A. Radcliffe, J.D. Stamatakis, R.J.C. Steele and G.T. Williams *Surgical Epidemiology and Audit Unit, Royal College of Surgeons of England*

Accurate and comprehensive histology reports of colorectal cancer specimens is critically important in establishing prognosis, the need for adjuvant therapy and for comparative audit. We have examined the content of pathology reports of 1242 resected colorectal cancers from the Welsh Colorectal Cancer Study and audited this against criteria set in previously agreed reporting guidelines.

The results show that only 11·3 per cent and 4 per cent of reports on colonic and rectal tumours respectively contained all items of information required by the guidelines. However, these low figures were increased to 78·0 per cent of colonic and 46·6 per cent of rectal tumour reports using a revised minimum criteria set for an adequate report. Included in this set are histological type and differentiation, depth of tumour penetration, whether or not the resection ends were free of tumour and whether or not lymph nodes were involved. Comment on the deep (radial) resection margin was also included for rectal cancers. Specific deficiencies identified included reporting the number of lymph nodes involved by tumour and the deep (radial) resection margin in cases of rectal carcinoma. There was a wide variation in results from different units.

Further methods to improve the standard of pathology reporting of colorectal cancer need to be introduced.

Poster 062

Vesicocolic fistula – colonic resection, the key to a successful outcome

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The surgical management of a vesicocolic fistula (VCF) is not standardised and the outcome remains unsatisfactory (1). VCF is usually associated with colonic disease and a distal colonic stricture. We report the results of a prospective study of standardised surgical treament which aims to resect the diseased colon with primary anastomosis.

Twenty-two patients were treated between February 92 and February 95. Of these, 15 had diverticular disease, 4 carcinoma colon/cervix, 2 post-traumatic and one Crohn's disease.

At surgery 18 of the 22 patients (82 per cent) were treated by colonic/rectal resection with primary anastomosis; one of these 18 patients with carcinoma had an en-bloc partial cystectomy. Of the remaining 4 patients, 3 underwent Hartmann's procedure and one a pan-proctocolectomy and end ileostomy.

There was only one surgery-related death secondary to colonic ischaemia; operative mortality 4 per cent. The only other major episode of morbidity related to an intraperitoneal urinary leak in the patient who underwent partial cystectomy. There has been no recurrence.

These data suggest that resection of the diseased colonic segment with primary anastomosis is the optimal surgical treatment for the majority of patients with VCF. This can be achieved with minimal mortality and morbidity. The bladder component can be treated simply by insertion of an indwelling catheter in patients with benign disease.

Poster 063

No abstract received

Poster 064

Disconnection, pouch revision and reanastomosis after ileal pouch-anal anastomosis (IPAA)

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The aim was to determine the outcome of patients with dysfunctional pouches in whom disconnection of the IPAA, pouch revision and reanastomosis has been carried out.

Twenty-three patients (8 men) were studied. Functional problems included impaired evacuation (n = 15), excessive frequency (n = 4) and fistulas (n = 4).

At revision operation, the functional problems were found to be due to a long efferent spout (n = 9), a redundant or perforated blind limb (n = 6), a twisted pouch (n = 3) or other causes (n = 5). The pouch was salvaged in 14 patients and a new pouch was constructed in 9. Postoperative complications (all minor) occurred in 5 of 23 patients. Two patients underwent revision IPAA twice.

At median follow-up of 5 years (range 1–10), function is good in 11 patients, fair in 5 patients and 1 patient experiences recurrent pouchitis. Revisional surgery was unsuccessful in 6 of 23 patients (3 gross incontinence, 2 excessive bowel movements, 1 Crohn's). Their pouches were excised.

Revision of the pouch and IPAA can safely be undertaken with good results in carefully selected patients.

Poster 065

Paediatric restorative proctocolectomy

J.S. McCourtney, P.A.M. Raine* and I.G. Finlay *Department of Coloproctology, Royal Infirmary of Glasgow and *Department of Paediatric Surgery, Royal Hospital for Sick Children, Glasgow*

The role of restorative proctocolectomy (RP) in paediatric patients requiring surgical treatment for ulcerative colitis (UC) or familial adenomatous polyposis (FAP) has not been established. In this study 7 of 74 patients (9 per cent) who underwent RP at our institutions were 16 years of age or less at the time of pouch construction. We have compared this group with the adult patients in the series to assess differences in major postoperative morbidity and functional outcome.

Median ages of the two groups were 14 years (range 9–16) and 30 years (range 16–59). The paediatric group comprised 5 patients with a preoperative diagnosis of UC and 2 with FAP, compared with 59 UC and 8 FAP in the adult category. Median duration of follow-up was 14 months (range 10–60) in the paediatric group and 30 months (range 12–77) in the adult patients. There was no operative mortality. Morbidity following RP included pouchitis in 1 paediatric patient (14 per cent) requiring temporary diversion with a loop ileostomy. The adult morbidity included 4 pouch excisions (7 per cent); 4 pouch-anal anastomotic leaks (7 per cent); 4 pouch-anal stenoses (7 per cent) and 2 patients requiring loop ileostomy for severe pouchitis (3 per cent). The proportion of patients with major postoperative morbidity was similar in both groups: paediatric n = 1 (14 per cent) vs adult n = 14 (21 per cent) P = ns (Fisher's exact test). Median day and night stool frequencies were similar (Mann–Whitney tests applied): day – paediatric ×4 (×2–7), adults ×5 (×2–12) P = ns; night – paediatric 0 (0–2), adult ×1 (0–4) P = ns.

These data show that morbidity in paediatric patients undergoing RP is no greater than experienced by adult counterparts. RP in children is a safe procedure which gives satisfactory long-term functional results.

Poster 066

Simultaneous ambulatory assessment of anorectal and vesicourethral dysfunction

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Bladder and rectum share a common origin and nerve supply and have similar functions. Six patients were investigated with symptoms of urinary and faecal urgency/urgency incontinence by simultaneous ambulatory urorectodynamics, to determine their inter-relationship and whether there is a common aetiological factor.

Manometric changes from mid-anal canal, rectum, bladder and sphincteric urethra were recorded by pressure transducers connected to a portable recorder. Integrated EMGs of the striated anal and urethral sphincters were also recorded. Patients pressed an 'event marker' on the recorder and kept a diary.

A total of 131 hours' recording was obtained (mean 21 hours and 49 minutes). An unique phenomenon of instability showing simultaneous rectal and vesical pressure rise and an irregular rise and fall of the anal and urethral sphincter pressure with corresponding EMG activity, was seen consistently. Episodes of variable duration occurred in the day as well as during sleep. A minimum of 10 episodes were recorded during the day and 7 during the night.

This new technique has demonstrated instability in both the vesicourethra and anorectum which appears to be responsible for these symptoms. Since striated and smooth muscle are affected, the cause may be neurogenic and sited in the spinal cord.

Poster 067

Total mesorectal excision – assessment of the laparoscopic approach

J.E. Hartley, A. Qureshi, R. Farouk, G.S. Duthie, P.W.R. Lee and J.R.T. Monson *The University of Hull, Academic Surgical Unit, Castle Hill Hospital, North Humberside HU16 5JQ*

Routine total mesorectal excision (TME) during resection of low rectal cancer has produced the lowest reported rates of local recurrence. In most laparoscopic-assisted anterior resections the pelvic dissection is performed during the open phase of the operation. Doubt remains as to the ability of a pure laparoscopic rectal dissection to achieve TME. We have studied all patients undergoing curative surgery with TME prospectively in a non-randomised fashion – all laparoscopic procedures were performed by a single surgeon and conventional resections by a second consultant colorectal surgeon. The age, sex and median Dukes' stage of the two groups were comparable. Histological examination of the resected specimens was performed by a single colorectal pathologist, blinded to the method of resection, according to standard techniques. Results are presented as median value with interquartile range.

Group (*n*)	Specimen length (cm)	Long. margin (cm)	Radial margin (cm)	Positive margins	Lymph node yield
LAP (13)	25·0 (6·5)	3·5 (2·25)	0·6 (0·85)	0	7·0 (5·0)
OPN (12)	28·5 (11·0)	3·0 (1·5)	1·0 (1·2)	0	10·0 (4·5)

LAP = laparoscopic, OPN = conventional surgery.

These preliminary data confirm the technical feasibility of achieving TME laparoscopically, and suggest that immediate cancer clearance is not compromised. Further follow-up is required to determine the consequences for bladder and sexual function of this approach. Oncological safety will be assessed by long-term locoregional recurrence rates.

Poster 068

Management of the perineal wound in abdominoperineal resection of the rectum for carcinoma

J.A. Grabham and R.H.S. Lane *Royal Hampshire County Hospital, Winchester*

Despite the increasing number of patients with rectal cancer who have sphincter-saving resections, it seems likely that abdomino-perineal resection will remain the only suitable treatment for some patients. The principal morbidity associated with the procedure relates to the perineal wound and controversy persists regarding the best surgical techniques and methods of management. We report a series of 33 consecutive patients who underwent AP resection for cancer by one consultant surgeon.

The indications for AP resection included cellular differentiation, extent of local spread, perforation and concomitant disease. The mean distance of the tumour from the anal margin was 5·4 cm. The peritoneal floor was reconstituted following resection but the levators were not approximated. The perineal wound was closed primarily in all cases. Suction drains were placed in the presacral space. The buttocks were approximated using an adhesive dressing and the patients nursed lying on their side.

Uncomplicated primary healing occurred in 31 (94 per cent) of perineal wounds. One pelvic abscess required drainage and one wound broke down. Both subsequently healed. There was one chronic sinus and one perineal hernia.

The significant morbidity of perineal wound failure can be minimised by effective drainage of the presacral space and particular attention to reducing stresses on the perineal wound.

Poster 069

Pouch salvage: long-term outcome

S. Korsgen and M.R.B. Keighley *University Department of Surgery, Queen Elizabeth Hospital, Birmingham*

We have analysed the outcome of 39 pouch salvage procedures in 211 patients having restorative proctocolectomy (RP) between 1984 and 1994; ulcerative colitis (UC; *n* = 145), Crohn's disease (CD; *n* = 10), indeterminate colitis (IC; *n* = 6), familial adenomatous polyposis (FAP; *n* = 28), megacolon (M; *n* = 12) and chronic constipation (C; *n* = 8). There were 11 operations for pouch perineal (*n* = 3; UC) or pouch vaginal fistulas (*n* = 8; 6UC, 1CD, 1C) all arising from the dentate line. Salvage was uniformly successful for the 6 vaginal fistulas where there was no underlying CD or IC. Attempts to clear pouch perineal fistula were uniformly unsuccessful, all had anorectal sepsis prior to pouch construction. There were 8 operations for pouch cutaneous fistulas (7UC, 1M) but 3 involving the ileoanal anastomosis failed. Three patients had pouch construction after conservative proctocolectomy (3UC), all were successful but all suffer from soiling. Four patients have had attempted salvage for chronic sepsis at the ileoanal anastomosis (3UC, 1IC), only 1 has been successful. Three patients have had strictures in, or just above the pouch treated by strictureplasty (1UC, 1CD, 1M), all were successful. Two patients with a long efferent limb (1CD, 1UC) have been treated by excision and anastomosis, both were successful. One pouch prolapse was successfully treated by pouch pexy (1UC). Three patients who lost their original pouch from ischaemia had a new one constructed (3UC), all have had a poor result and now live with an ileostomy. Four patients had secondary surgery for incontinence (pelvic floor repair 3, graciloplasty 1; 1UC, 2M, 1C), only 2 were successful.

Most reoperations for pouch salvage are successful provided there is no chronic sepsis at the ileoanal anastomosis.

Poster 070

Wessex colorectal cancer audit – variations in presentation with tumour site

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A population-based audit is in progress in the Wessex region (population 3·1 million). Between September 1991 and February 1995, 4887 cases of colorectal cancers were diagnosed. Data were analysed to compare differences in patterns of presentation for tumours in different parts of the colon. The sites of tumours were grouped into caecum and ascending colon (right side), hepatic flexure and transverse colon (transverse), splenic flexure descending and sigmoid colons (left side) and rectum and rectosigmoid junction (rectal).

Rectal tumours occurred more often in men and presented at an earlier age than right-sided tumours. In men, 46·7 per cent of cases were rectal compared with 35·6 per cent in women; the trend was reversed for right-sided lesions (18·6 per cent of tumours in men, 26·7 per cent in women). For rectal tumours, 26·5 per cent were under 65 years old, compared with 18·5 per cent of right-sided tumours.

Only 14·1 per cent of rectal tumours presented as emergencies in contrast with 33·8 per cent of tumours proximal to the splenic flexure. For elective referrals, physicians tended to see right-sided disease (39·3 per cent of right-side tumours) whereas surgeons were referred the left-sided disease (84·1 per cent of rectal tumours). The duration of symptoms reported to the general practitioner was longer for rectal tumours (median 78 days) than right-sided tumours (52 days). Right-sided lesions were more commonly associated with a reduced haemoglobin (65·6 per cent of cases) than rectal lesions (27·8 per cent). Despite the variations in length of symptoms, right-sided cancers presented at a later stage (5·3 per cent Dukes' A) than rectal lesions (18·3 per cent Dukes' A). They were also more often poorly differentiated (26·5 per cent and 12·9 per cent respectively).

All the reported differences are statistically significant.

Poster 071

An evaluation of laparoscopic surgery for colorectal cancer

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A prospective comparison of laparoscopic or laparoscopic-assisted colorectal resection (LR) versus open resection (OR) has been undertaken in order to evaluate early benefits and cost implications.

During a 19-month period consecutive patients with colorectal cancer underwent either elective LR (n = 22) or OR (n = 26). Indications for open resection were: gross obesity, synchronous tumours, tumour fixation, a palpable mass (>7 cm) preoperatively, or transverse colectomy.

LR was attempted in 26 patients and completed in 22, four being converted and amalgamated with the OR group. One death occurred in an OR patient. Median hospital stay was shorter in the LR group: 7·5 versus 12 days. Average morphine requirements were less in the LR patients: 15 mg/day versus 28 mg/day and their recovery was generally more rapid. Port site or wound recurrences have not occurred but one pelvic recurrence has been observed following palliative open rectal surgery. Although operation time was longer and the instrument costs higher for LR, this was offset by a shorter hospital stay and overall costs were not significantly different between the two groups.

This study suggests that when LR of colorectal cancer is possible, early recovery is substantially improved.

Poster 072

Total rectal mucosectomy preserves sensation after restorative proctocolectomy

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Introduction: Restorative proctocolectomy has become the operation of choice for ulcerative colitis. The functional results, however, are imperfect and the complication rate high. The sensation of rectal distension (dependent in part on the presence of the rectum) is important in the control of defaecation. Rectal sensation is detrimentally affected following restorative proctocolectomy. A new modification of restorative proctocolectomy, conserving the whole of the rectal muscular and serosal layers, in order to improve perception of rectal distension and filling, has been studied.

Methods: In seven patients with ulcerative colitis and one with slow transit constipation, following total colectomy, the rectum was mobilised from the pelvis, sparing the superior rectal vessels, and divided at the pelvic floor. The rectum was then opened, a mucosal proctectomy was performed throughout its length, and then it was wrapped around an ileal J pouch, which was stapled to the anus. A defunctioning ileostomy was raised. The patients were assessed functionally and physiologically before and after (mean 15·2 months, range 8–22) the procedure by questionnaire, manometry and balloon distension.

Results: The procedure was completed in six of the eight patients, being abandoned in two for difficulty in performing the mucosectomy and inaccessibility in a small pelvis. There was no postoperative mortality. Pelvic sepsis developed in two patients, both required operative drainage. Two patients have retained their ileostomies, one at own request. Identical, pelvic perception of rectal distension was retained both in response to the pouch filling with faeces and to artificial distension.

	n	Preop (range)	Postop (range)
24 h freq.	4	6·3 (0·14–8)	5·3 (1–10)
Continence score (max. 55)	4	49 (40–55)	45 (33–51)
Max. squeeze pressure	6	186 cm H_2O (147–240)	160 cm H_2O (90–210)
First constant sensation	6	63 ml (13–160)	61 ml (19–150)
Desire to defaecate	6	118 ml (60–320)	89 ml (30–180)

Conclusion: Conservation of the rectal muscular and serosal layers maintains the sensations of rectal distension and filling and may lead to improved pouch function.

Poster 073

Failure of lateral internal sphincterotomy for the treatment of chronic anal fissure is due to technical failure

R. Farouk, J. Gunn, P.W.R. Lee and J.R.T. Monson *Academic Surgical Unit, University of Hull, Castle Hill Hospital, Hull*

Lateral internal sphincterotomy has become the treatment of choice for chronic anal fissure. Between 1 and 5 per cent of patients experience failure of the fissure to heal after surgery. We have assessed thirteen patients [8 women; median age 34 (range 17–56) years] with persistent anal fissure after sphincterotomy by endoanal ultrasound and anal manometry.

The median resting anal pressure in these patients was 115 (98–138) cm H_2O. Endoluminal ultrasound revealed partial division of the internal anal sphincter in two patients. The remaining eleven patients had an intact internal anal sphincter but had ultrasound evidence of division of the external anal sphincter at the site of previous surgery.

All thirteen patients subsequently underwent a second lateral internal sphincterotomy with resolution of their symptoms. The postoperative resting anal pressures fell to 89 (74–101) cm H_2O ($P < 0.01$; Rank Wilcoxon Test).

Failure of the original sphincterotomy would appear to relate either to inadequate internal sphincterotomy, or to inadvertent division of the external anal sphincter. Endoanal ultrasound allows accurate assessment of these patients to determine why failure of treatment occurs.

Poster 074

MRI appearances of desmoids in familial adenomatous polyposis

J.C. Healy, S.K. Clark, R.H. Reznek, P. Armstrong and R.K.S. Phillips *St Mark's Hospital, London and St Bartholomew's Hospital, London*

Intra-abdominal desmoid tumours are an important source of morbidity and mortality in familial adenomatous polyposis (FAP), and are one of the two commonest causes of death in patients who have had a prophylactic colectomy for this condition. CT is currently the imaging modality of choice for diagnosis and follow-up, but the use of MRI has not been widely reported for intra-abdominal desmoid tumours. MRI is superior to CT in evaluating musculoskeletal desmoids, and its signal intensities reflect the cellularity of the tumours, which may determine the rate of progression.

We have performed abdominal and pelvic axial MRI and CT scans on 14 FAP patients known to have desmoids. The results document the range of appearances demonstrated on MRI, compared with CT, to detect the lesion. The characteristics of the tumours at different sites are also compared. Follow-up scans relate the intensity of the T2 weighted image to subsequent tumour growth.

Although desmoid disease can run a severe course, prolonged periods of stability and even regression have been reported. Imaging which avoids the use of ionizing radiation and which may offer some prognostic information would be of great value in managing this difficult problem.

General/Urology

Poster 075

Comparative assessment of surgical training using objective criteria

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The aims of this study were to develop and validate an objective method of assessing surgical trainees' operative experience.

Operative activity in a surgical unit was retrieved from a prospectively recorded computer database for a three-year period. Operations were weighted using intermediate equivalence (IE) values. The number of operations performed (caseload), IE workload, consultant involvement and a subjective assessment of ability by the three consultants were obtained for each of 3 SHO III and 7 SHO I. Total caseload correlated poorly with subjective grading. Total workload correlated well with subjective assessment of the SHO III, and the total workload excluding minor operations correlated well with subjective assessment of the SHO I. The SHO IIIs' workload had a higher percentage of complex procedures than SHO Is' and for both grades the degree of complexity increased during the year of tenure. A consultant was the assistant in 50 per cent of the intermediate and major operations performed by the SHO I in the first quarter of each post, dropping to 30 per cent in the remaining three quarters.

Objective assessment was easily performed and interpreted whilst retaining a sufficient degree of sophistication to present complex activities.

Poster 076

Is antibiotic prophylaxis indicated for open-groin hernia repair?

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Antibiotic prophylaxis is not used routinely for non-implant, 'clean' surgery. However, Platt *et al.*[1] reported a statistically significant benefit to patients receiving cefonicid compared with placebo in a study of 1218 patients undergoing groin hernia repair and non-implant breast surgery. We have sought to substantiate this finding in a multicentre, double-blind, prospective study in which patients received co-amoxiclav 1·2 g or placebo. Five hundred and sixty-three (91 per cent) of 619 patients undergoing open-groin hernia repair completed the protocol: 283 received co-amoxiclav and 280 placebo. There was no difference between the groups in the number of patients receiving local or general anaesthetic; the type of repair performed; the use of a subcutaneous fat suture; the type of skin closure used; the use of wound analgesia; or use of a wound drain.

Twenty-five (9 per cent) patients in both groups sustained a wound infection. This is a higher incidence of infection than anticipated and shows no benefit in favour of prophylaxis. The incidence of infection according to the centre in which the study was performed, or the other variables recorded, showed no significant variation.

Antibiotic prophylaxis is of no benefit in patients undergoing open-groin hernia repair. The high incidence of infection requires further investigation.

1. Platt *et al.* Perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery. N Engl J Med 1990; 322: 153–60.

Poster 077

Do surgical wards need an 'arrest' team?

S.T. Williams and J.R. Nash *Derbyshire Royal Infirmary, London Road, Derby*

The aim of the study was to review the efficacy of the 'arrest' team attending cardiac arrests on surgical wards. Over a two-year period 50 arrest calls were made from the general surgery, urology and orthopaedic wards. Thirty-one patients did not respond to resuscitation and a further 7 died before leaving hospital. Of the remainder, half of the calls were unnecessary as the team was not required. Only 6 (12 per cent) of the calls resulted in successful cardio-pulmonary resuscitation (CPR).

Failed resuscitation:

7 (age 67–93, average 82) had a serious underlying disease;
9 (age 61–87, average 85) had asystolic arrest;
9 (age 68–88, average 77) had electromechanical dissociation;
5 (age 77–81, average 78) had ventricular fibrillation and
1 had a respiratory arrest.

In the resuscitated group:

6 did not require any treatment from the 'crash' team;
7 (age 27–90, average 74) died before leaving hospital and
6 (age 54–82, average 72) were discharged.

The hospital does publish indications for CPR in the junior doctors' handbook but these are frequently not followed. More selective use of the team is likely to increase successful outcome and improve the enthusiasm of its members for attending arrests on surgical wards. Nurses feel obliged to attempt CPR and call the arrest team unless it is clearly recorded in the notes to the contrary. Doctors always need to include this decision in their care plan.

Poster 078

Hazards of electrocautery smoke in colorectal surgery

P.M. Sagar, A. Meagher, S. Sobzcak and B.G. Wolff *Mayo Clinic and Mayo Foundation, Rochester, MN, USA*

Electrocautery is widely used in colorectal surgery. This exposes both surgeon and assistants to variable amounts of smoke. To date, the composition and hazards of this smoke have received little attention.

Six patients were studied. Each underwent colorectal resection with electrocautery. A small-calibre plastic tube was attached to the cautery pencil to extract the smoke which was collected in Tenax collecting media. Fifty samples of smoke were collected from each patient. Chemical analysis was carried out with gas chromatography and mass spectrometry. Samples were tested for volatile organic compounds (including polycyclic aromatic hydrocarbons), nitrosamines and nitrites.

Significant levels of the carcinogen benzene ($70\,\mu g/m^3$) and the hepatotoxins ethylbenzene ($36\,\mu g/m^3$), styrene ($21\,\mu g/m^3$) and toluene ($460\,\mu g/m^3$) were detected. These substances may pose a health hazard on prolonged exposure.

Conclusion: Smoke generated by use of electrocautery is potentially harmful. Further investigation is needed to define and reduce this risk.

Poster 079

Changes in microvessel density during human wound healing

J.H. Salaman, B. Jasani* and K.G. Harding *Wound Healing Research Unit and *Department of Pathology, University of Wales College of Medicine, Cardiff*

The use of microvessel density (MD) as an index of tumour angiogenesis is well recognised. In this study MD has been quantified during human wound healing.

Following biopsy at operation, sequential 6-mm punch biopsies were taken from the edge of granulating, surgical excision wounds in 5 patients. Microvessels were visualised with an anti-human Factor VIII antibody. A light microscope at ×250 magnification was used for all counts which were made in triplicate. Each first count was made immediately below the leading epithelial edge. Whole field counts were then made vertically downwards to the cut end of the section. These were likewise repeated 1 field behind and in front of the first field. For the operative biopsies MD was determined in the area of highest vascularity.

No statistical difference was found between counts from the 3 areas, these data were therefore pooled. MD showed an inverse relationship with the depth below the leading edge. There was a significant decrease in mean (±SD) MD between 0 mm (27·65 ± 12·69) and 4·76 mm (15·15 ± 9·97) $P = 0{\cdot}05^*$ below the leading edge in all biopsies. To standardise the healing time for all patients, MD was calculated at 25 per cent, 50 per cent and 75 per cent of total healing time (T). There was a significant increase from operation to 25 per cent T and 50 per cent T with a significant decrease between 50 per cent T and 75 per cent T ($P < 0{\cdot}05^*$). (*Students t-test.)

These data illustrate consistent temporal and spatial changes in MD during healing and may provide a useful tool for the study of non-healing wounds.

Poster 080

Electronic log-book – evaluation of trainees and training posts

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Since the end of the 1980s it has been a requirement of the Royal Colleges of Surgeons for trainees to keep log books of their surgical experience. The current practice of keeping written records makes it difficult to collate, analyse and hence audit either the trainee or the training post.

We present a surgical log system based on a desk-top computer (PC or Mac) that interfaces with Psion and Newton hand-held computers. It is also possible to interface with some hospital information programs. For ease of use it incorporates icon and button drives through a graphical windows interface and includes an on-line help facility.

In addition there is a powerful reporting function allowing analysis factors including: fitness of patient, type/subtype of procedure, level of supervision, urgency of procedure, time operation was performed, presence and nature of complications, suture/prosthetic material used. Comprehensive lists are included for each of the above categories enabling 'point and click' selection, whilst permitting personal addition to each list.

With the trend towards shortening surgical training under the Calman recommendations, there is a requirement for a system which enables accurate data retrieval and analysis in a form that is useful for the evaluation of the surgical trainee and for the evaluation of surgical training posts.

Poster 081

Use of abdominal ultrasound for the diagnosis of intra-abdominal injury in severely injured patients

I.M. Bain, M. Braithwaite, P. Oakley and R.M. Kirby *North Staffordshire Hospital, Stoke on Trent*

Clinical examination alone is inadequate for the assessment of abdominal injury in severely injured trauma patients. Diagnostic peritoneal lavage (DPL) was regarded as the gold standard for the diagnosis of these injuries, but recently abdominal ultrasound has been shown to have similar sensitivity.

We have studied prospectively our use of DPL and ultrasound in the management of trauma patients at this hospital from 1992 to 1995, concentrating on severely injured patients (ISS $>$ 15, RTS $<$ 7·8404, admitted to ITU).

	1992–1995
Severely injured	764
Ultrasound	200
DPL + US	20
DPL	52

The sensitivity and specificity of abdominal ultrasound in all 220 severely injured patients for the detection of free fluid and/or organ injury were 82·7 per cent and 99·5 per cent respectively. The sensitivity was increased to 89·1 per cent by repeat scanning. In comparison the sensitivity and specificity of DPL were 82·8 per cent and 97·2 per cent respectively. No patients died as a result of a false negative test. Non-therapeutic laparotomies were significantly commoner after DPL, 9/25 (36 per cent) compared to 3/23 (13 per cent) after US ($P < 0{\cdot}05$ Fisher's exact). Abdominal ultrasound is now the first-line investigation at this centre for evaluation of possible intra-abdominal injury in trauma patients, as it is non-invasive, quick and repeatable.

Poster 082

Risk of late perforation in blast intestinal contusions

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Injury due to blast waves is an emerging battlefield hazard. The dominant intestinal injuries in survivable lung injury are multiple intramural haematomas (IH) which are subject to unheralded, delayed perforation as long as 14 days after injury. Small bowel and colon are equally affected. Immediate intestinal perforations may be sustained but contusions are most likely to be discovered incidentally at laparotomy.

Sixteen anaesthetised pigs were exposed to mild blast overpressures. One hundred and eighty-eight IH were examined histologically at either 1 or 24 hours. Correlation of histological grade of injury with external appearances indicated that small bowel contusions larger than 15 mm were injured significantly more severely than smaller IH (Chi^2 = 8·15, 2 d.f.; $P < 0{\cdot}05$). Colonic contusions larger than 20 mm were at a greater risk of perforation than smaller IH (Chi^2 = 14·95, 2 d.f. $P < 0{\cdot}001$). Using these discriminators in favour of guidelines from previous workers reduces the number of IH needing excision from 86·5 to 60·4 per cent for small bowel and 72·9 to 27·2 per cent for the colon.

Examination of the histological features shows that intestinal injury starts at the mucosa and spreads towards the serosa. Serosal injury is ominous and indicates that such contusions should be excised to prevent late intestinal perforation. Using these guidelines will allow safe surgical management of blast-injured casualties.

Poster 083

Abdominal wall hernias in polycystic kidney disease

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Clinical experience in the management of patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) led to the observation that this group of patients has a high incidence of abdominal wall hernias. We reviewed the notes of all patients with ADPKD on the Renal Replacement Therapy Database which includes haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD) and transplanted (Tx) patients and compared them to non-ADPKD renal failure patients and a control group of general surgical patients.

	ADPKD	Non-ADPKD	Control
Total number	85	85	85
M:F	39:46	39:46	39:46
Mean age (range)	59 (23–74)	57 (29–75)	56 (21–83)
Form of renal therapy	CAPD: 14 HD: 11 Tx: 60	CAPD: 14 HD: 11 Tx: 60	
Number of hernias	28 inguinal 6 incisional 7 paraumbilical	5 inguinal 1 incisional 1 paraumbilical	3 inguinal
Total hernias	41	7	3
Incidence of hernias	48 per cent	8 per cent	3·5 per cent

This study suggests that there is a significantly increased incidence of all abdominal wall hernias in patients with ADPKD compared with both the general population and other patients with impaired renal function.

Poster 084

Metastatic tumours of the parotid gland

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Twenty patients (12 males, 8 females) with metastatic parotid tumours presenting over a 12-year period were retrospectively evaluated. The median age at operation was 69 (r = 17–88) years. Preoperative tests included fine needle aspiration cytology (11) and CT/MRI scans (14).

Most tumours originated from the head and neck region, the two main types being squamous cell carcinoma (10) and malignant melanoma (7). All 20 presented with a parotid mass and half had associated lymphadenopathy. Eleven (55 per cent) patients underwent superficial parotidectomy and the remainder being distributed almost equally between total conservative (5) and radical (4) parotidectomies. Neck dissection was required in 75 per cent of patients. Only those patients with clinically palpable lymph nodes had tumour-positive neck dissection specimens. Half of all patients recieved adjuvant postoperative radiotherapy.

Three-quarters of the patients are still alive after a mean follow-up of 31 months and only one has developed a marginal recurrence. The cumulative five-year survival rate was 51·1 per cent (SE = 0·17; Kaplan-Meier method). There was no significant difference (P = 0·48, log rank statistic = 0·50) in the three-year survival rates of patients undergoing radical versus modified/functional neck dissection. Patients undergoing superficial parotidectomy had a longer overall survival compared to total/radical parotidectomy (P = 0·04, log rank statistic = 4·03), perhaps reflecting the advanced nature of tumours requiring the latter excision.

It is concluded that superficial parotidectomy is usually an adequate operative treatment for secondary parotid tumours, and proposed that not all patients suspected of parotid gland metastatic disease require neck dissection if they have no palpable lymph nodes and have a negative MRI scan. It appears that no survival advantage is conferred by undertaking radical over modified or functional neck dissection.

Poster 085

Which surgical patients do not survive?

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Studying surgical mortality may indicate ways to improve services. We report on surgical deaths during 1994 in South East Scotland, where 99 per cent of surgical deaths are audited.

Two hundred and ten patients (21 per cent) were admitted for terminal care alone. Among 782 patients treated actively: median age was 75 years and 305 (40 per cent) were aged >80 years; 626 (80 per cent) were admitted as emergencies and 655 patients (84 per cent) had at least one comorbid factor. The commonest diagnosis was mesenteric ischaemia. Surgery was not undertaken in 311 patients (active medical decision, n = 121), and was abandoned on finding a terminal situation in 63/296 patients (18·per cent). Intensive care was used before operation in only 66 cases (12 per cent) and after operation in 197 cases (46 per cent).

Surgeons believed management could have been improved in 160/593 cases (27 per cent), most frequently by better preoperative management (13 per cent), decision to operate (13 per cent) or better postoperative care (11 per cent). Choice of operation, technical aspects of surgery and experience of staff were less frequently considered sub-optimal. Preoperatively, the surgeon believed the risk of death to be high in 63 per cent of cases. In 65 operated patients (14 per cent) the risk of dying was perceived to be considerable, the patient was over 80 years and at least 2 comorbid factors were present.

Most surgical mortality now arises in elderly patients with comorbid disease who present as an emergency. Improvements might be made in their perioperative management.

Poster 086

A randomised trial of topical NSAID for infusional thrombophlebitis during peripheral parenteral nutrition

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Phlebitis is the commonest complication of peripheral parenteral nutrition (PPN) and is thought to be secondary to local chemical irritation and inflammation. To assess the effects of a topical non-steroidal anti-inflammatory drug (NSAID) preparation on its incidence, a randomised, double- blind, placebo-controlled clinical study was performed. All patients had heparin (333 iu/l) added to the infusate, and a 5-mg glyceryl trinitrate patch applied distal to a 20f intravenous cannula. Only the first cannula used was studied. Patients in the treatment arm (n = 21) had 2 ml of traxam gel applied over the cannulation site, with an inert gel applied in the control group (n = 28). The cannulation sites were covered with a occlusive dressing and were inspected twice daily for signs of phlebitis.

Phlebitis requiring cannula removal developed in 34 of the cannulation sites. The mean time to onset was 53 hours. The mean volume infused was 6·12 litres. There was no significant difference between the mean values in the treatment and control groups (54 h vs 52 h, 6·35 l vs 5·94 l).

This study shows that the high incidence of infusional thrombophlebitis during PPN does not appear to be substantially reduced by topical NSAID therapy.

Poster 087

Free radical scavenging by lazaroids improves renal blood flow during sepsis

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Introduction: Intrarenal vasoconstriction is a major factor in the genesis of sepsis-associated renal failure. Oxygen-derived free radicals (ODFR) are known to mediate renal injury after ischaemia-reperfusion and are increased during sepsis. Antioxidants improve survival from experimental sepsis, but the role of ODFR as mediators of renal dysfunction during sepsis is unclear. Lazaroids (U74389G) are antioxidants which inhibit ODR-induced lipid peroxidation. We hypothesised that ODFR contribute to bacteraemia-induced alterations of the renal microcirculation.

Methods: Rat hydronephrotic kidneys were studied by videomicroscopy. Interlobular (ILA) arteriolar diameter and flow, afferent (AFF) and efferent (EFF) arteriolar diameters, and cardiac output (CO) were measured at

15 min intervals for 120 min. U74389G or vehicle (VEH) was infused prior to a bolus of live *Escherichia coli* (EC) or saline (NS).

Results: Infusion of EC caused preglomerular vasoconstriction (ILA, AFF) and hypoperfusion despite increased cardiac output. Both constriction and hypoperfusion were significantly attenuated by U74389G. Data are expressed as per cent change from baseline, mean ± SEM, at 60 min; n = 5–8 per group.

	CO	ILA	Flow	AFF	EFF
NS	1·0 ± 1·8	–0·7 ± 1·2	–0·2 ± 2·5	1·5 ± 1·2	0·0 ± 1·3
LAZ	5·4 ± 5·3	–1·9 ± 0·7	–1·5 ± 3·2	0·3 ± 1·1	–1·1 ± 0·7
EC + VEH	47·9 ± 1·9*	–28·5 ± 5·6*	–58·3 ± 9·9*	–23·2 ± 5·2*	–2·5 ± 2·5
EC + LAZ	40·8 ± 15·2*	–8·4 ± 1·8†	–21·7 ± 7·4†	–5·6 ± 1·5†	1·9 ± 2·2

* $P < 0·05$ vs NS. †$P < 0·05$ vs EC + VEH by ANOVA & Tukey Kramer HSD test.
LAZ = lazaroids.

Conclusion: Inhibition of lipid peroxidation by U74389G improved renal blood flow during sepsis, suggesting that ODFR are involved in the microvascular response to bacteraemia. Lazaroids may prove an effective agent in preventing sepsis-associated renal dysfunction.

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The British Journal of Surgery (ISSN 0007-1323) is published monthly. All subscriptions are entered on a calendar-year basis, beginning in January and expiring the following December. Back issues are available, please contact us for details.
Subscription rates for Volume 83 (1996) are:

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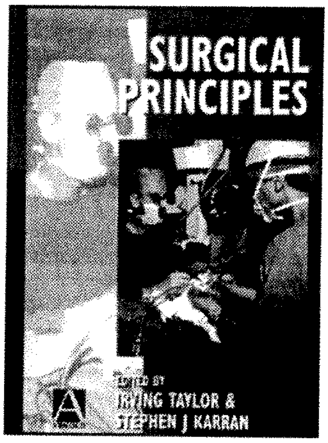

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Chairman &
Editor in Chief
G. J. A. Clunie

ISSN 0004-8682
Published monthly

Editors
J. Ludbrook
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British Journal of Surgery 1996, 83, 881–882

Leading articles

Colonic pouches in the treatment of low rectal cancer

Despite the well proven improved functional results following the construction of a colonic J pouch–anal anastomosis for cancer of the lower rectum, the procedure has not found widespread use outside specialized colorectal units. This may be because of technical difficulties with ultra-low anterior resection and unfamiliarity with pouch construction in general surgical departments. But is the colonic J pouch–anal anastomosis mandatory for patients with carcinoma of the lower rectum? Total mesorectal excision is essential in achieving a low local recurrence rate in low rectal cancer; such excision, however, must be followed by total rectal resection. The complete mobilization of the rectum required for total mesorectal excision along with division of the lateral ligaments devascularizes any remaining rectal remnant[1]. Preservation of any length of distal rectum following total mesorectal excision, even where this is oncologically permissible, leaves an ischaemic rectal stump with a significant risk of anastomotic breakdown[1,2]. In patients with a low rectal cancer, both total mesorectal and total rectal excision are, therefore, necessary.

Anal function following straight coloanal anastomosis may be crippling and may adversely affect lifestyle in as many as 40 per cent of patients. This is especially true in the first year following coloanal anastomosis when anal function is at its worst. It has already been well documented that the colonic J pouch–anal anastomosis has definite functional advantages over a straight coloanal anastomosis[3–9]. In a recently published prospective randomized trial, the advantages of colonic J pouch–anal anastomosis over straight coloanal anastomosis were evident even at 1 month after ileostomy closure; the former continued to be significantly superior 1 year after ileostomy closure[3]. At 1 month after ileostomy closure, 65 per cent of patients with a colonic J pouch passed three or fewer motions per 24 h, while it took 12 months for 70 per cent of patients with a straight anastomosis to achieve this frequency. By 12 months, 95 per cent of patients with a pouch were passing three or fewer motions per 24 h. No patient with a pouch needed antidiarrhoeal medication at any stage, whereas ten of 20 patients without a pouch needed antidiarrhoeal medication at 1 month and nine still needed it at 12 months after ileostomy closure.

Will colonic pouches lead to defaecatory difficulties with the need for enemas or suppositories to avoid faecal impaction, as had been reported in up to 25 per cent of patients with colonic pouches in one series[8]? I believe that routine excision of the sigmoid colon as well as the use of a short (7–8 cm) pouch are the key factors in achieving good long-term results without evacuation difficulties[3,9]. There are two reasons. First, no differences were noted in neorectal volume, compliance or rectal sensation between a descending coloanal and a descending colon pouch–anal anastomosis in a series from this institution, indicating that the pouch does not work via an increased reservoir volume function but, perhaps, via negation of propulsive movements within the pouched segment[9]. A small colonic pouch was sufficient for good function in this series[3,9], whereas large pouches may lead to defaecatory difficulties if they favour faecal retention because of pouch dilatation. Another possible problem of larger pouches is that the disturbed motility of a long segment of bowel may be too much for normal mass colonic movements to overcome; this is currently a subject of investigation in this department. The second consideration is that sigmoid colon may further contribute to evacuatory problems because of the severe motility dysfunction of a pouched sigmoid segment, compared with that of a descending or transverse colonic pouch. Postoperative defaecatory difficulties were noted in 25 per cent of patients in a series using sigmoid colon routinely for pouches[8], but not in the series from this hospital where the sigmoid colon is always removed[3,9].

Unlike in the situation of ileal pouch–anal anastomosis for familial adenomatous polyposis or ulcerative colitis, however, total rectal mucosectomy is not mandatory for low rectal cancer. It is needed only when a peranal hand-sutured coloanal anastomosis is being contemplated, a situation which should be rare in this condition. Rectal mucosectomy will not gain an extra margin of clearance for tumour eradication; if distal clearance after ultra-low anterior resection is considered to be inadequate, coloanal techniques are not suitable and total anorectal ablation should be performed instead. A triple-stapled colonic J pouch–anal anastomosis[3] is the best technique for colonic pouch construction for low rectal cancer as it is faster to perform and anal function is generally better with stapled anastomosis than with endoanal hand-sutured anastomosis, as anal sphincter damage is minimized and sensitive rectal mucosa preserved.

In patients for whom postoperative adjuvant chemotherapy and/or radiotherapy is necessary, the colonic J pouch continues to maintain superior function over a straight coloanal anastomosis without increased morbidity[9]. The colonic J pouch–anal anastomosis is not contraindicated in patients who are to undergo postoperative radiotherapy.

In conclusion, the colonic J pouch is important if optimal early postoperative anal function is to be achieved. This is especially desirable in older patients and in those with a limited life expectancy, for whom good results from the outset are essential to ensure a good quality of life. Attention to intraoperative detail is mandatory if good function is to result in the long as well as the short term.

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British Journal of Surgery 1996, 83, 883–884

Antibiotic prophylaxis in severe acute pancreatitis

Since the appearance of a Leading Article on infection in acute pancreatitis in the Journal in December 1994[1], there have been significant advances in our understanding of the role of antibiotic prophylaxis in this area. The 1994 leader summarized the experimental evidence for the penetration of modern antibiotics into pancreatic tissue and pancreatic juice. It also described the results of an Italian randomized multicentre clinical trial, which showed a reduction in pancreatic sepsis, but not mortality rate, amongst patients with severe acute pancreatitis given imipenem[2]. Recent evidence from clinical studies has supported the value of antibacterial prophylaxis in severe acute pancreatitis and it now seems incontrovertible that antibacterial prophylaxis should be part of standard therapy in this condition.

An experimental study[3] has examined the value of gut decontamination. Severe pancreatitis was induced in mice by feeding a choline deficient, ethionine supplemented diet; antibiotics were introduced after 36 h. Oral antibiotics improved survival after 48 h, and a combination of oral polymyxin B, amikacin and amphotericin B produced significantly better survival at 7 days than all other treatments. However, at 10 days the survival rate, although higher with this regimen, was not significantly different from that associated with other antibiotics or controls. Bacterial translocation was reduced by the antibiotics and the authors concluded that there are theoretical grounds to support antibiotic prophylaxis in clinical practice.

Another experimental study[4] examined the efficacy of cefotaxime administered from 12 h after the induction of pancreatitis in cats, by means of intrapancreatic administration of *Escherichia coli*. Pancreatic infection developed in eight of 11 animals that received no antibiotic, but in none of the nine animals receiving cefotaxime. Cefotaxime reached bactericidal levels in both pancreatic tissue and pancreatic juice. These two studies both suggest that antimicrobial therapy may be helpful in prophylaxis against pancreatic infection in severe acute pancreatitis.

There are now available three clinical studies that demonstrate the value of antibacterial prophylaxis in severe acute pancreatitis. A Dutch study[5] randomized 102 patients to standard therapy, or standard therapy with selective decontamination of the intestinal tract with oral colistin, amphotericin and norfloxacin. In addition, a paste containing these three agents was applied to the mouth, tracheostomy (if present) and rectum. Sodium cefotaxime was given intravenously to the selective decontamination group. Selective decontamination reduced the overall mortality rate through its significant effect on Gram-negative pancreatic infection and late mortality. The number of laparotomies per patient was reduced in the group receiving selective decontamination.

Workers in Finland[6] used a simpler regimen of intravenous cefuroxime in high doses, started at the time of admission. A randomized study of 60 patients with alcohol-induced severe acute pancreatitis showed a reduction in the mean number of infectious complications (1·0 *versus* 1·8) and deaths (one *versus* seven) in 30 patients allocated to antibiotic prophylaxis. This study suggests that systemic antibiotic treatment with an agent that can eliminate translocating bacteria may be sufficient to prevent colonization of necrotic tissue. More expensive agents known to penetrate better into pancreatic tissue may be unnecessary.

A third study, from France[7], included 23 patients with acute alcoholic pancreatitis with two or more fluid collections. These patients were randomly allocated to no antibiotic treatment or to prophylactic treatment with ceftazidime, amikacin and metronidazole for 10 days. Seven episodes of severe sepsis occurred among 12 patients in the former group; no infection occurred in patients receiving prophylactic antibiotics. Of the seven patients with infection, three died; there was one death in the group receiving antibiotics.

It is believed that pancreatic infection in severe acute pancreatitis arises as a result of bacterial translocation from the gut which permits colonization of the

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Presented to a Pancreatic Section Symposium at the British Society of Gastroenterology, Brighton, UK, March 1996 necrotic tissue. The above three clinical studies suggest that the phase of translocation is amenable to antibiotic prophylaxis. It is debatable whether selective gut decontamination is necessary, since the protocol in the Dutch study also included systemic antibiotic treatment, which may, in itself, be sufficient to prevent translocation and colonization.

Most advances in the management of acute pancreatitis have arisen from general improvements in intensive care and system support. Patients with severe acute pancreatitis who recover from their illness have a good long-term prognosis[8] and their treatment is cost-effective[9]. Any specific measure that improves prognosis and is likely to reduce mortality is, therefore, very worthwhile. There is now convincing evidence that early antibiotic prophylaxis is beneficial and this should form part of the standard treatment of patients identified as having severe acute pancreatitis, either by specific inflammatory markers or by scoring systems, such as the Glasgow or Acute Physiology And Chronic Health Evaluation (APACHE) II scores. Attention should now be directed to determining what is the most appropriate and cost-effective antibiotic prophylaxis. Before selective gut decontamination is widely adopted, its benefits should be compared with those of systemic antibiotics alone.

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British Journal of Surgery 1996, 83, 885–892

Review

Choice of prophylactic surgery for the large bowel component of familial adenomatous polyposis

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The surgical options for treating the large bowel component of familial adenomatous polyposis are total proctocolectomy, colectomy with ileorectal anastomosis, and restorative proctocolectomy, with or without mucosectomy. Although the first of these eradicates all mucosa at risk, it carries several disadvantages, not least of which is a permanent ileostomy. There is little to choose functionally between the other two operations. The choice should be based on the perceived risk of cancer developing in any residual rectum; the factors influencing this risk are discussed.

Recent studies[1] have revealed that colorectal tumorigenesis is a multistep process associated with the accumulation of several genetic changes whose total, rather than order with respect to each other, is responsible for determining the biological properties of the tumour. Mutations in at least four or five genes are required for the formation of a malignant tumour, while fewer changes suffice for benign tumorigenesis. Losses of 5q21 alleles are the earliest genetic somatic alterations yet identified in 20–50 per cent of sporadic colorectal carcinomas and in about 30 per cent of colorectal adenomas as small as 5 mm in diameter[2,3]. In familial adenomatous polyposis (FAP), an autosomal dominant disorder, a germline alteration of a gene on the long arm of chromosome 5 is inherited[2–4] that may be responsible for the hyperproliferative epithelium present in these patients. FAP is characterized by the formation of hundreds of adenomas in the stomach, duodenum, ileum, colon and rectum. The phenotype becomes evident in puberty; the large bowel and duodenum are the sites of greatest predilection.

The familial nature of FAP and its localization to the large bowel were first noted by Cripps[5] in 1882. Attention was subsequently drawn to the occurrence of colorectal cancer[6] and, more recently, to the development (more frequent than in the general population) of cancer in other organs; these include the duodenum, pancreas, biliary tree, small intestine, stomach[7] and brain[8,9]. The association with desmoid disease has been noted[10] and recently reviewed[11,12]. FAP is lethal if left untreated because colonic adenomas inevitably undergo carcinomatous change, usually by the fifth decade of life.

FAP is among the most common inherited diseases predisposing to cancer, affecting about 0·01 per cent of Japanese, British and American populations[13]. The mutation frequency is between 1 and 8 per 29 000 births[14].

Medical management

There is evidence that regression of colorectal and duodenal adenomas, occasionally complete, can be achieved by long-term use of non-steroidal anti-inflammatory drugs (NSAIDs)[15–20], both in patients with an intact colon and after colectomy with ileorectal anastomosis (IRA)[15,20,21]. In a randomized trial, sulindac therapy was associated with a reduction in epithelial cell proliferation in the duodenum and with a trend toward adenoma regression[20]. In the same group of patients, rectal adenomatosis responded more dramatically, showing both marked reduction of cell proliferation and significant regression of adenomas. In another study of similar design[21], the action of the drug on mucosal proliferation proved to be more erratic; rectal adenomas reduced in number but not in size, possibly because inhibition of cell proliferation was lost as polyps enlarged. Indomethacin, a sulindac analogue, delivered in the rectal remnant of patients who failed to show polyp regression after colectomy, induced almost complete regression in both number and size of adenomas within 1–3 months[22]. However, as with sulindac[21], prevention of recurrent adenomas requires long-term maintenance treatment[22]. Sulindac is, therefore, a possible treatment for patients in whom rectal polyps have failed to show significant spontaneous regression after IRA and who are unsuitable for pouch surgery. It may be useful in patients with an intact colon to reduce the number and size of polyps and to delay surgery, if desirable, or to clear the rectum before colectomy. Sulindac therapy may also be useful in early duodenal polyposis or as an adjunct after duodenal clearance[20]. However, caution should be exercised in assuming that a reduction in the number of polyps is proof of a lower risk of cancer in patients with FAP.

Following treatment with NSAIDs 'the residual rectal adenomas are usually small, flat and pliable; therefore distension of bowel with air sometimes makes detection difficult'[16]. Niv and Fraser[23] reported prevention of adenoma recurrence by sulindac in a patient who subsequently developed invasive carcinoma despite regular surveillance, raising the question of whether cancer may arise *de novo* in some patients with FAP.

Among NSAIDs, attention has been recently focused on aspirin and the reduction of the colonic cancer mortality rate related to regular aspirin use[24,25]. Risk reduction seems to be dose related[26]. In 1993, the European Concerted Action for Polyposis Prevention

Paper accepted 19 January 1996

started a study aimed to test the effect of aspirin and dietary factors (resistant starch) on number and size of rectal polyps, and on colonic crypt cell proliferation rate in patients still having an intact large bowel. The study involves many national and regional polyposis registers co-ordinated by the Division of Human Genetics of the University of Newcastle upon Tyne, UK.

There is also evidence that oral calcium reduces rectal cell turnover in patients with FAP after colectomy[27], but it has no clear effect on number, size or distribution of rectal adenomas.

Although it is not known how NSAIDs or calcium act[24,25,27,28], their effect on benign colonic tumours in those with FAP provides a clear illustration of control of a genetic abnormality leading to cancer. However, at present, medical treatment is unlikely to replace colectomy as the primary therapy[19].

Surgery

The earliest surgical procedures were carried out for symptomatic patients presenting with cancer. Prophylactic colectomy, to eradicate most of the mucosa at risk, was not proposed until the mid-1920s, with establishment of the Polyposis Register at St Mark's Hospital in London, and following the first colectomy with IRA[29] in 1918. In the 1940s colectomy with IRA became the preferred procedure over total proctocolectomy with ileostomy for patients without rectal cancer[30,31]. More recently, restorative proctocolectomy (RPC) with ileal reservoir formation has been recommended as the first choice in most cases[32].

Available operations

Conventional proctocolectomy is today rarely used; it is applicable in patients with cancer of the lower rectum (*Table 1*). In most cases the surgical decision lies between colectomy with IRA and RPC. This choice will depend on many considerations, including technical factors, complications, function and, most of all, the perceived long-term risk of cancer developing in the rectum or ileal reservoir. To date, there is little information on the latter; we do, however, know a considerable amount about rectal cancer after IRA.

Whatever surgical procedure is chosen, current practice is to operate at 15–20 years of age, when the risk of cancer is less than the 3·3–4 per cent reported in patients 25 years old[33,34]. However, it is possible that this aspect of management may change in the light of the developments in medical management described.

Operative morbidity and mortality

Colectomy with IRA is a comparatively simple one-stage procedure, with exceedingly low rates of mortality and morbidity[35–37] (*Table 2*). Since the pelvis is not dissected, sexual function is not at risk[35,37]. RPC is more complex. Although the mortality rate is also very low[36–38], specialist training is required to perform this operation[35]. Pelvic dissection is necessary and this leads to a greater local complication rate (pelvic abscess, minor anastomotic defects, pouch–vaginal fistula and intra-abdominal bleeding)[36,38]. Septic complications, in particular, should be avoided, as they are the commonest reason for failure[38]. Defunctioning ileostomy, when carried out for technical reasons or to mitigate the consequences of pelvic sepsis, should it occur, has its own associated morbidity[39]. The recent trend to perform RPC without a covering ileostomy has yielded good clinical and functional results, at the expense of complications requiring an ileostomy – usually temporary – in about 15 per cent of cases[40–43]. It may increase the attractiveness of this procedure over IRA. The duration of hospital stay after each operation is about the same.

Table 1 Surgical options for the large bowel component of familial adenomatous polyposis

Procedure	Advantages	Disadvantages	Indications
Total proctocolectomy	Eradicates all mucosa at risk	Pelvic and perineal dissection Sepsis/?nerve injury Difficult wound healing Permanent ileostomy	Cancer of lower rectum at diagnosis
Colectomy with ileorectal anastomosis	Acceptable function Normal continence Simple operation No pelvic dissection No ileostomy One-stage procedure	Risk of rectal cancer Requires lifelong surveillance	Age <30 years Absence of symptoms Spared rectum ? Desmoid at colectomy Metastatic cancer of colon or upper rectum at colectomy
Restorative proctocolectomy with mucosectomy	Eradicates all mucosa at risk Acceptable function Acceptable continence ? One-stage procedure	Pelvic dissection Sepsis/?nerve injury Mucosectomy ? impaired continence	Age >30 years Presence of symptoms Uncontrollable rectal adenomas Poor compliance to follow-up Family history of rectal cancer Non-metastatic cancer of colon or upper rectum at colectomy
Restorative proctocolectomy without mucosectomy	Acceptable function Near-normal continence ? One-stage procedure	Pelvic dissection (as above) Retained mucosa Requires surveillance	Age <30 years Absence of symptoms Spared rectum

Table 2 Complications and function following surgery for familial adenomatous polyposis[35,36]

	St Mark's Hospital, 1977–1989 ($n = 99$)		Mayo Clinic, 1978–1988 ($n = 115$)	
	RPC ($n = 37$)	IRA ($n = 62$)	RPC ($n = 94$)	IRA ($n = 21$)
Complication rate (%)	57	21	26	17
Relaparotomy rate (%)	24	3	5	6
Frequency per 24 h	4·5 (2–15)*	3 (1–11)*	5(2)†	4(2)†
Urgency (< 15 min) (%)	17	50	—	—
No. of night evacuations	43	10	1(1)†	1(1)†
Normal continence (%)	60	72	87	83
Fulguration of rectal polyps (%)	—	44	—	61

RPC, restorative proctocolectomy; IRA, colectomy with ileorectal anastomosis. There were no deaths in either series. Values are *median (range) and †mean(s.d.)

Cancer prevention effectiveness

Surveillance of the rectal stump after colectomy with ileorectal anastomosis

After colectomy with IRA there is a reduction in rectal mucosal cell proliferation[44] and evidence exists which suggests that rectal adenomas can regress spontaneously[45–47]. Spontaneous regression, either partial or total, significantly correlates with the number of adenomas at the time of colectomy[47]. Thus, at a mean follow-up of just over 6 years after operation, only half of patients require fulguration[36,37]. Rectal adenomas may, however, reappear and degenerate in the same patient[47,48].

It has become accepted practice[49] to examine the rectal stump by rigid endoscopy at intervals of 6 months. Whether this is an appropriate frequency is not known, but patients who fail to attend for surveillance beyond 2 or more years and develop rectal cancer are likely to have an advanced lesion[47,50]. In patients with a rectal stump length of 15 cm or less, spontaneous regression of adenomas and surveillance may possibly delay the onset of rectal cancer by around 10 years, compared with those whose stump is longer than 15 cm not attending for follow-up[50,51].

Surveillance of the rectal stump, with diathermy destruction of adenomas, can reduce the number of expected rectal cancers by 85 per cent[52] but carries a significant complication rate of about 3 per cent[49]. The commonest complication is bleeding, usually manageable conservatively. Death has occurred but the mortality rate is well below 1 per cent[49].

Rectal cancer risk after colectomy with ileorectal anastomosis

Moertel *et al.*[53] followed 143 patients after colonic resection and reported a rising incidence of rectal cancer with the duration of follow-up (*Table 3*). In a subsequent report of the same patients 10 years later, rectal cancer had occurred in 32 per cent at 20 years and in 55 per cent at 30 years[54]. At the time, no other study with such a long follow-up was available and it was, therefore, difficult to judge whether these high rates were a manifestation of the true natural history or whether other factors were responsible. For example, some of the patients had a significant length of sigmoid colon left behind, more than 40 per cent of patients had no family history and regular surveillance of the rectum was carried out in only about half of the patients. Bulow[55] in 1984 reported the cumulative risk of cancer developing in 58 patients of the Danish Polyposis Register undergoing colectomy with IRA by the end of 1982. In this group of patients, with a mean follow-up of 3 (range < 1–19) years and median length of rectal stump 15 (range 8–25) cm, the risk at 5 years was 3·5 per cent (95 per cent confidence interval (c.i.) 0–10·3 per cent) and at 10 years 13·3 per cent (95 per cent c.i. 0–70·3 per cent).

Recently, Iwama *et al.*[56] in a follow-up of 320 Japanese patients receiving colectomy with IRA, reported a cumulative incidence of rectal cancer similar to that published by authors from the Mayo Clinic and the Danish Register[55] (*Table 3*). There are, however, several possibilities of bias. For example, three-quarters of the patients were symptomatic at presentation and one-third had colonic cancer at diagnosis (10–20 per cent in other series[50,51]). Some patients had a significant length of sigmoid colon retained, the length of follow-up, the surveillance policy and cancer-related mortality rate were not stated, and the number of patients followed for more than 15 years was small. Other studies, based on information from national registers and series from specialized centres[48–51], which have an adequate length of follow-up and similar surveillance policy, have reported lower incidence rates (*Table 3*).

It is interesting that the cancer risk after IRA in some populations[48–51] is similar to that found 10 years earlier in others[53–56] (*Table 3*). In 224 patients treated at St Mark's Hospital, the mean age at colectomy was 26 (median 24) years and that at the diagnosis of rectal cancer was 48·3 (range 28–67) years, giving a mean interval of 13·5 (range 1–37) years (*Table 4*). Age at IRA, above or below 25 years, was not a predictor of the subsequent risk of rectal cancer[51]. Another recent series[50] of 1363 patients, reported by the multicentre Leeds Castle Polyposis Group, describes remarkably similar findings. The mean age at colectomy was 27 years and the mean age at diagnosis of cancer 46 (range 18–67) years, with a mean interval of 13·4 (range 0·1–36) years (*Table 4*). In contrast, in the Mayo Clinic series[53] the mean age at surgery was 36 years, 10 years later, but the mean age of cancer onset was the same (48 years) (*Table 4*). These data suggest that the chronological age and not the number of years of follow-up is the important risk factor.

Data from St Mark's Hospital[51] and the Scandinavian Study[50], based on 224 and 294 patients respectively, show that after colectomy with IRA the cumulative probability of rectal cancer developing by the age of 50 years ranges between 5·2 and 10·0 per cent (95 per cent c.i. 1·2–9·2 and 4·5–16·0 per cent respectively). By age 60 years the respective risk is between 14·1 and 29·0 per cent (95 per

Table 3 Cumulative risk of cancer of the rectal stump after colectomy with ileorectal anastomosis for familial adenomatous polyposis: review of major series

Centre	Year	No. of patients	Follow-up (years) 5	10	15	20	25	30
Mayo Clinic[53]	1970	143				32·2	59	
St Mark's Hospital[88]	1975	89					3·6	
Mayo Clinic[54]	1980	143	5	14	19	32	40	55
Danish Register[55]	1984	58	3·5	13·3				
St Mark's Hospital[49]	1985	174		5	8		13	
Cleveland Clinic[48]	1987	133		4		12		
St Mark's Hospital[51]	1992	224					15	
Scandinavian Study[50]	1992	294	3·1	4·5	5·7	9·4	13·1	
Japanese Register[56]	1993	320	4	13	23	37		

Risk values are percentages

Table 4 Age of onset of rectal cancer in patients with familial adenomatous polyposis

	Year	Proportion with rectal cancer*	Mean (range) age at diagnosis (years)	Mean age at colectomy (years)	Mean (range) interval from colectomy (years)
At presentation					
St Mark's Hospital[88]	1975	141 of 263 (53·6)	39	—	—
After colectomy with ileorectal anastomosis					
Mayo Clinic[53]	1970	46 of 143 (32·2)	48	36	—
St Mark's Hospital[51]	1992	22 of 224 (9·8)	48·3 (28–67)	26	13·5 (1–37)
Leeds Castle Polyposis Group[50]	1992	50 of 1363 (3·7)	46·0 (18–67)	27	13·4 (0·1–36)

*Values in parentheses are percentages

cent c.i. 4·1–24·1 and 18·0–40·0 per cent respectively). There is, therefore, a threefold increase in risk of rectal cancer developing between the ages of 50 and 60 years. The inference from these data must be that patients over the age of 45 years who wish to retain the rectum after IRA should undergo more intensive screening[51]. Furthermore, prophylactic restorative proctectomy should be seriously considered after the age of 50 years.

Thus the cancer risk is mainly related to the age of the patient; the longer the follow-up the greater the incidence. Other factors play a part, however. These include the number of rectal adenomas[47,57] at the time of colectomy. In patients with fewer than 20 rectal adenomas, a risk of 10 per cent at 15 years was reported compared with more than 30 per cent in those with 100 or more[54]. There is, perhaps, a threefold increased risk of subsequent rectal carcinoma in patients presenting at the time of colectomy with colonic carcinoma[53,54]. However, this increased risk is not confirmed by data from the Japanese Register[57] and the Scandinavian Study[50]. Patients with a rectal stump longer than 10 cm[57] or 15 cm[48,50,54] are at increased risk of cancer developing. Particular genetic factors may also be important. Recently, a type of mutation in the *APC* gene has been described that is associated with a particularly severe phenotype of FAP[58]. Gastrointestinal symptoms and death from colorectal cancer occurred in patients with this mutation about 10 years earlier than in those with other mutations. A clinically attenuated form of polyposis, characterized by a small number of adenomas and late onset, has also been described[59]. Identification of the type of mutation in individual families may, therefore, modify management, by influencing the choice of prophylactic surgery and type of surveillance.

Death from rectal cancer after colectomy with ileorectal anastomosis

In patients who develop rectal cancer there is a high chance of salvage with a good prospect of long-term survival. Eleven of 174 patients undergoing colectomy with IRA followed for a median of 12 (range 1–14) years at St Mark's Hospital developed a metachronous rectal cancer[49]. Four tumours were of Dukes stage A and only three patients died from cancer. Similar results have been reported by others[47,48,50], with Dukes stage A lesions in about 50 per cent of cases and a cancer-related mortality rate of 10–30 per cent. Following colectomy with IRA, the death rate from rectal cancer is low, ranging from 1 to 2 per cent at 10 years and from 2 to 4 per cent at 15 years[34,49,50]. At 30 years it is still under 5 per cent[50]. The cancer-related survival rate of affected patients is 71–78 per cent at 5 years[50,51] and 55 per cent at 10 years[51].

Rectal excision after colectomy with ileorectal anastomosis

Cancer of the rectal remnant is not the main reason for removing the rectum after colectomy with IRA. In a population of 297 patients from the Scandinavian Study[50], 25 years after colectomy the rectal stump had been removed in 47 (15·8 per cent). In 34 (11·4 per cent) of these, the indication was multiple large adenomas, severe dysplasia, stricture and incontinence; in only 13 patients (4·4 per cent) was the indication cancer (*Fig. 1*). Secondary restorative proctectomy can be offered to most of these patients, unless there is cancer in the lower rectum, faecal incontinence or intra-abdominal desmoid[36,60]. The functional results differ slightly from those of RPC as first operative procedure[60].

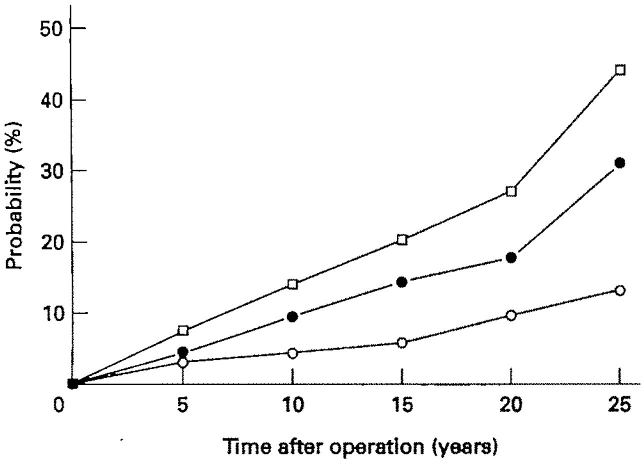

Fig. 1 Cumulative probability of excision of the rectal stump for cancer (○), for other reasons (●) and overall probability (□) after colectomy with ileorectal anastomosis for familial adenomatous polyposis[50]

Surveillance of the ileal pouch after restorative proctocolectomy

Over the past two decades reports of adenomas in the small bowel, whether in a terminal ileostomy[61], above an IRA[61,62], in a continent reservoir[63], or in the neorectum following colectomy with straight or reservoir ileoanal anastomosis[64–66], have increased. Rarely, adenocarcinoma associated with ileal adenomas has developed at the ileostomy site many years after proctocolectomy[67–69]. So far, there is no evidence of an increased risk of small bowel adenoma after RPC[66]. However, follow-up is short and the malignant potential of small bowel adenomas in patients with polyposis is not known.

Recently, invasive adenocarcinoma has been reported at the ileoanal anastomosis following RPC[70]. The most likely origin of this tumour was from residual rectal mucosa, although the terminal ileal mucosa could not be excluded with certainty. Adenomas are found in anorectal mucosal 'strippings' in almost all cases of FAP[71]. The increasing tendency to perform totally stapled RPC, a less demanding procedure[41,72] which in almost all cases leaves behind anorectal mucosa containing microadenomas even when transection is performed at the 'dentate line'[73], theoretically puts these patients at risk of cancer developing at the ileoanal anastomosis. Although this risk does not seem as great as that of rectal cancer following IRA, periodic endoscopic evaluation would seem prudent until more information becomes available.

Pouchitis due to acute inflammation of the reservoir mucosa occurs in 5–30 per cent of patients following RPC for ulcerative colitis[74]. It is, however, very rare in patients with FAP[74,75]. Recently, two cases of pouchitis have been reported in patients with FAP[76], showing concurrently the features of ulcerative colitis in the operative specimen. There is no evidence to date to suggest that pouchitis should be a significant clinical consideration when deciding between RPC and IRA.

Function

Frequency of defaecation and night evacuation (*Table 2*) are slightly better after IRA than after RPC[36,37]. Other end-points, including anal irritation, dietary restriction, antidiarrhoeal medication, quality of life and continence, are little different. There is less urgency of defaecation after RPC[36], but one study has reported a higher incidence of night incontinence[37].

Causes of death after prophylactic colectomy

Rectal cancer is a relatively uncommon cause of death after colectomy with IRA. Of 174 patients observed by Bussey *et al.*[49], only three died from rectal cancer, whereas three died from desmoid tumour and six from upper gastrointestinal neoplasm. In an updated review from St Mark's Hospital of 197 patients observed between 1948 and 1987, only four have died from rectal carcinoma whereas nine have died from upper gastrointestinal cancer[77]. In the Cleveland Clinic series[78], 36 patients died after prophylactic colectomy between 1915 and 1987. Desmoid tumours accounted for 11 deaths, periampullary carcinoma for eight and rectal cancer for three. In the Leeds Castle Polyposis Group multicentre study[7], at a median age of 52 (range 17–81) years 36 (2·9 per cent) of 1255 patients with FAP developed periampullary invasive carcinoma, with a relative risk 300 times greater than that in an age-matched general population. Of these 36 patients, 21 had died at a median follow-up of 60 months and four had residual disease. Similar increased relative risks of duodenal and ampullary adenocarcinoma were recently described[79]. Iwama *et al.*[56] reported standardized (observed/expected) mortality ratios of 250 for duodenal carcinoma and 210 for colorectal carcinoma.

Thyroid cancer, mainly of papillary type and affecting young women, occurs 22·6–160 times more frequently among patients with FAP than in normal individuals[56,80]. However, the prognosis of this carcinoma appears to be good, as the standardized mortality ratio is nil[56,80].

Desmoid tumours develop in a relatively high proportion (10–32 per cent) of patients with FAP[12,56,81], especially in that subset who also display the extracolonic manifestations defined in Gardner's syndrome[82–84], and in familial clusters[12,56]. In these patients desmoid tumours are mostly intra-abdominal[12,82], involving the mesentery of the small bowel[85]. Their occurrence increases with age until the fifth decade of life[12]. They are found more frequently in women of child-bearing age and usually develop following colectomy[12,82,84,86]. Surgical cure is rare because of the difficulty of complete excision[85] and tendency to local recurrence[82,84]. Their associated mortality rate seems high (10 to 70 per cent), with a young age at death, commonly below 40 years[12,56].

Thus, prevention of large bowel cancer by colectomy has allowed these patients to live longer and to develop neoplasms at other sites. After prophylactic colectomy with IRA, the risk of subsequent death from upper gastrointestinal cancer or desmoid disease is greater than the risk of death from cancer of the retained rectal segment[49,87]. So far no difference exists in terms of other causes of death between patients having IRA and those having RPC. Patients remain at a greater than threefold risk of dying compared with the general population and the relative risk is greatest for women[87]. The main difference is that death from rectal cancer generally occurs within 5 years of diagnosis as opposed to death from other causes[50].

Conclusions

After colectomy with IRA there is a significant incidence of rectal cancer. The risk seems to be related to the number of rectal adenomas, to the length of the rectal stump, to the presence of colonic cancer at colectomy, and to the type of *APC* gene mutation; it rises with the age of the patient. In patients who attend for regular follow-up this risk appears to be low with a low cancer-specific mortality rate. RPC, theoretically able to abolish the development of large bowel cancer, is obviously attractive. Because rectal cancer after colectomy with IRA is only one cause of death in patients with FAP, RPC will make only a small contribution to the reduction in mortality rate.

There is little to choose functionally between the two operations. The choice should be based on the perceived risk of cancer developing in the rectum. Certain factors exist that might influence this (*Table 1*).

There is a strong indication for RPC for patients with a substantially increased risk of rectal cancer. These include those over 30 years of age and those presenting with symptoms or uncontrollable rectal adenomas. For patients with an already established non-metastatic cancer of the colon or upper rectum, for whom there is a strong family history of rectal cancer or long-term follow-up cannot be assured, RPC is indicated.

Patients with metastatic cancer of the colon or upper rectum at diagnosis and those with desmoid tumours at colectomy or family history of such[37] should be treated by colectomy and IRA.

Asymptomatic patients under the age of 30 years, with a relatively spared rectum, may be offered colectomy with IRA. The length of rectal stump should not exceed 10–15 cm and subsequent surveillance must be assured. Perhaps medical treatment by oral calcium supplementation or NSAIDs may control the growth of adenomas and lead to a reduction in the future development of rectal carcinoma. Only careful follow-up over time will tell.

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New member of the Editorial Board

Another surgeon from overseas has joined the Editorial Board of the Journal during 1995/96. A short synopsis of his biographical data and clinical interests is presented.

DR JULIO DIEZ
(Argentina)

Dr Julio Diez (born 1935) is a surgeon at Hospital de Clinicas San Martin in Buenos Aires. He qualified as a doctor in 1959 from the National University of Buenos Aires and trained as a resident at the University Hospital. In 1968 he obtained a WHO Scholarship to study in the USA. He has served on the Executive Committee of the Argentine Academy of Surgery. His particular interest is in HPB Surgery, and he is President of the Argentine Chapter of the International HPB Association.

Please note that the synopsis of new members appearing in the May 1996 issue incorrectly spelt Professor Vladimir Fedorov's name. The Journal apologizes for this error.

British Journal of Surgery 1996, 83, 893–901

Review

Repeated liver resection for recurrent liver cancer

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Patients with cancer recurrence limited to the liver alone after a first liver resection may be candidates for a repeat resection. Some 191 second and ten third liver resections for recurrent colorectal metastases, and 128 second and ten third liver resections for recurrent hepatocellular carcinoma (HCC), were evaluated after reviewing the literature. The 5-year survival rate after second liver resection for colorectal metastases was 26 per cent with a median survival time of 30 months. Mortality and morbidity rates were 1·2 and 27·4 per cent respectively. The 5-year survival rate after second resection for HCC was 40 per cent with a median survival time of 40 months. The operative mortality rate was 2·3 per cent; morbidity occurred in 13 per cent of patients with HCC. Survival after primary colorectal resection was significantly better for patients with metachronous metastases than for those with synchronous disease; survival correlated with a long interval between the first and second liver resection (in both colorectal liver cancer and HCC). Repeated liver resection may be performed in selected patients and yield a similar survival to that obtained after first liver resection.

Surgical resection has been regarded as the only treatment that may offer potential cure of both metastatic and primary liver cancer. However, liver resection with radical intent is restricted to a minority of patients and, overall, the prognosis is still poor. Only about 5 per cent of patients presenting with colorectal liver metastases have been considered candidates for curative surgery[1–3]. The resectability rate for hepatocellular carcinoma (HCC) is not more than 20 per cent[4,5]. These figures reflect a potential delay in diagnosis, and stress the importance of a search for new diagnostic techniques, surveillance after colorectal resection and screening for endemic HCC. Progress in these aspects might increase the proportion of patients for whom a curative liver resection is possible. Advances in diagnostic measures, such as ultrasonography and computed tomography, together with improvements in operative techniques and perioperative care, have encouraged a more aggressive approach, with an increased rate of liver resection during the past two decades[2,5,6].

Liver resection for colorectal metastases results in a 5-year survival rate of about 25–35 per cent[1–3]. The 5-year survival rate after resection for HCC may reach 30–50 per cent[5,7–10]. Unfortunately, the majority of patients in both groups will sooner or later have recurrence of disease, usually leaving only non-curative therapy. Nevertheless, a small number of patients with recurrence appear to have localized potentially resectable disease confined to the liver alone.

During the past 10 years several reports have appeared, usually with a limited number of cases, describing patients with liver cancer subjected to a second or even a third liver resection. After a review of the literature, the collected series and case reports were studied to evaluate repeated liver resection for both colorectal liver metastases and HCC. The focus was on long-term results, but operative mortality and morbidity rates were also assessed. Furthermore, features of possible prognostic importance after resection of the primary colorectal cancer, and after the first and second hepatectomies, were sought. Although the patients in the present analysis were treated in different institutions over a long period of time and patient data in some instances were incomplete, we feel that this review of the literature provides valuable information on repeated liver resection.

Methods and analysis

Colorectal carcinoma

Patients identified by Medline literature search who were subjected to a repeat liver resection for colorectal liver metastases, and for whom subsequent follow-up data were available, were included in the protocol. Only curative or at least intended curative resections were entered in the study; palliative and incomplete resections were excluded. A positive resectional margin was defined as tumour growth present within a certain distance from the cut surface, usually 1 cm. The policy concerning patients considered free from disease, but with positive margins, was to include them. This is justified by their limited number and the problem of individual identification[11–14].

In 12 additional patients, surgery for extrahepatic disease was performed simultaneously with, or after, the second liver resection for colorectal metastases[13,15–21]. These operations included resections of lung metastases ($n = 8$) and diaphragmatic tumour extensions ($n = 3$), one ileal resection, one adrenalectomy for recurrent tumour, one biopsy of a pelvic wall recurrence followed by external radiation therapy, and one negative exploratory laparotomy. Because of the removal of all detectable disease at the time of the second liver resection, these patients were included in the study. In 32 patients only the mean survival after the second liver resection for colorectal liver cancer was defined[22,23]. Two patients with colorectal liver disease, who died within 1 month of operation[17–19], were also entered in the study.

Eventually a total of 194 patients with colorectal liver cancer were included from 24 reports[11–34], each contributing a median of six (range one to 28) patients. Follow-up after the second liver resection was recorded for 191 of the 194 patients and data concerning a third liver resection were available for ten patients. *Fig. 1* shows age and sex distribution in 108 patients with colorectal liver disease for whom data were available. Mean age at primary colorectal resection in the 64 men and 44 women was 57 years; the median age was 58 (range 27–75) years. There was no significant age difference between the sexes.

Paper accepted 8 February 1996

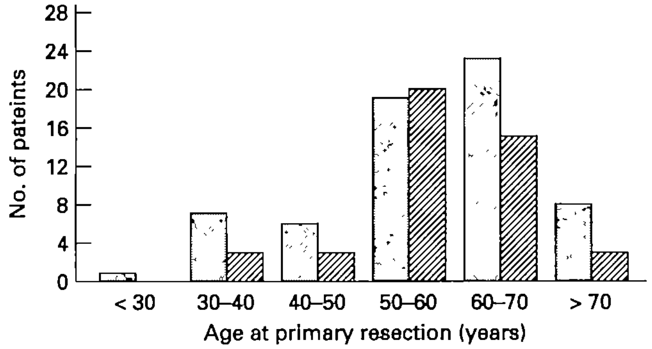

Fig. 1 Age and sex distribution in 108 patients who underwent second liver resection for recurrent colorectal metastases. Age at primary resection is shown. ☐, Men; ▨, women

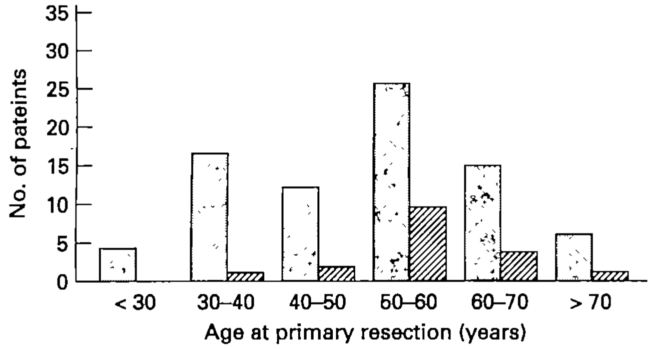

Fig. 2 Age and sex distribution in 95 patients who underwent second liver resection for recurrent hepatocellular carcinoma. Age at first resection is shown. ☐, Men; ▨, women

Hepatocellular carcinoma

The same selection procedure was used for patients operated for recurrent HCC. However, three palliative resections were not excluded as the identity of the patients concerned was uncertain[35]. Eleven patients with a huge HCC, who underwent a planned reresection or so-called two-stage operation[16,36,37], were excluded. Three patients were recorded as operative or postoperative deaths[16,34,38].

This resulted in 128 patients with HCC, derived from 15 reports[16,33–46], each report contributing a median of eight (range one to 21) patients. Of the 128 patients who underwent a second resection, ten were subjected to a third resection and also followed up. Mean age at first liver resection for HCC in 79 men and 16 women was 52 years; the median age was 54 (range 18–77) years (*Fig. 2*). Women tended to be older than men, mean age 57 and 51 years respectively, although this difference was not significant.

Data were collected from both groups of patients concerning isolated liver recurrence after the first liver resection, resectability rates, the relative proportion of repeated liver resections of the total number of curative resections, and the extent of resection. Survival following repeated liver resection was calculated by the Kaplan-Meier method[47]. The log rank test[48] was used to assess the effect of various features on survival. A P value of less than 0·05 was considered statistically significant.

Results

Colorectal carcinoma

Some 33–48 per cent of patients with recurrence after a first liver resection for colorectal metastases had disease confined to the liver alone (*Table 1*). In 15–33 per cent of these patients a second liver resection was performed. Radical reresections for recurrent disease represented 3–11 per cent of all radical liver resections performed (*Table 2*). The extent of the first and second resection was known in 131 patients, derived from 15 reports[11–15,17,19,20,24,26,28,30,31,33,34] (*Table 3*). At the first resection, these patients underwent 37 (25 per cent) lobectomies, 35 (24 per cent) segmentectomies, and 76 (51 per cent) subsegmentectomies or less. At the second resection, they underwent 42 (30 per cent) lobectomies, 39 (27 per cent) segmentectomies and 61 (43 per cent) subsegmentectomies or less.

Nine reports defined data about morbidity after the second resection for colorectal metastases[11–15,18–20,28]. Twenty-nine (27·4 per cent) of 106 patients had 31 postoperative complications altogether (*Table 4*). The most frequent complications originated from either the biliary system ($n=7$; e.g. biliary fistula $n=3$, bile leakage

Table 1 Disease confined to the liver alone as a percentage of recurrent disease and resectability rates of isolated liver disease

Reference	Year	Recurrence in liver only (%)	Resectability rate (%)
Colorectal metastases			
Lind *et al.*[31]	1992	42	33
Nordlinger *et al.*[24]	1987	41	29
Hohenberger *et al.*[27]	1990	48	21
Stone *et al.*[11]	1990		26
Butler *et al.*[32]	1986	33	15
Bozzetti *et al.*[15]	1992		26
HCC			
Kanematsu *et al.*[38]	1988	82	12
Suenaga *et al.*[45]	1994	89	24
Capussotti *et al.*[44]	1994	72	23
Ikeda *et al.*[42]	1993	91	22

HCC, hepatocellular carcinoma

Table 2 Curative repeated liver resection as a percentage of the total number of curative procedures

Reference	Year	(%)
Colorectal metastases		
Lind *et al.*[31]	1992	9
Nordlinger *et al.*[24]	1989	7
Butler *et al.*[32]	1986	3
Bozzetti *et al.*[15]	1992	7
Tomás-de la Vega *et al.*[22]	1984	10
Lange *et al.*[33]	1989	11
Griffith *et al.*[17]	1990	8
Fowler *et al.*[14]	1993	10
Overall		8·1
HCC		
Matsuda *et al.*[35]	1993	12
Kanematsu *et al.*[38]	1988	4
Nagasue *et al.*[39]	1986	9
Suenaga *et al.*[45]	1994	13
Ikeda *et al.*[42]	1993	10
Lange *et al.*[33]	1989	14
Zhou *et al.*[43]	1993	14
Overall		11·8

HCC, hepatocellular carcinoma

Table 3 First and second liver resections in 131 patients with colorectal metastases and 121 patients with hepatocellular carcinoma according to the extent of resection

	Colorectal metastases		HCC	
Extent of resection	First resection	Second resection	First resection	Second resection
Lobar resection	37 (25)	42 (30)	41 (33)	6 (5)
Left lobectomy	12	11	15	2
Extended left lobectomy	2	0	0	0
Right lobectomy	20	28	21	4
Ext. right lobectomy	3	3	5	0
Segmental resection	35 (24)	39 (27)	31 (25)	30 (24)
Trisegmentectomy	4	11	3	0
Bisegmentectomy	25*	11†	13¶	14**
Unisegmentectomy	4‡	13§	9	11
Unknown	2	4	6	5
Subsegmental resection	76 (51)	61 (43)	52 (42)	87 (71)
Total	148	142	124	123

Values in parentheses are percentages. *Including 15 left lateral segmentectomies (II, III); †including two left lateral segmentectomies (II, III); ‡including two resections of the quadrate lobe (IV); §including one resection of the quadrate lobe (IV) and two resections of the caudate lobe (I); ¶including eight left lateral segmentectomies (II, III); **including 11 left lateral segmentectomies (II, III). HCC, hepatocellular carcinoma

Table 4 Postoperative complications and morbidity in 35 of 152 patients who underwent second resection for either recurrent colorectal liver metastases or hepatocellular carcinoma

	No. of complications after second resection	
Complication	Colorectal metastases	HCC
Biliary system	7	1
Biliary fistula	3	1
Bile leak	3	
Biliary tract stenosis	1	
Intra-abdominal abscess	6	1
Subphrenic abscess	4	
Subhepatic abscess	1	1
Not specified	1	
Respiratory complication	7	
Pleural effusion	4	
Not specified	3	
Wound infection	3	
Haemorrhage	2	
Ascites	1	
Liver failure	2	
Thrombophlebitis	1	
Congestive heart failure	1	
Bacteraemia	1	
Bacterial peritonitis		1
Unknown		3
Total	31	6
Morbidity rate	29 of 106 (27·4)	6 of 46 (13)

Values in parentheses are percentages. HCC, hepatocellular carcinoma

Table 5 Extent of use and type of adjuvant therapy after second liver resection for colorectal metastases

Reference	Year	No. of patients	Type of adjuvant therapy
Griffith *et al.*[17]	1990	16 (67)	Systemic chemotherapy
Bozzetti *et al.*[15]	1992	3 (44)	Hepatic artery and systemic chemotherapy
Vaillant *et al.*[12]	1993	6 (43)	Intraperitoneal chemotherapy
Fowler *et al.*[14]	1993	2 (38)	Radiation therapy
Fong *et al.*[20]	1994	1 (40)	Immunotherapy
		1	Cryotherapy
Overall		29 (45)	

Values in parentheses are percentage of patients receiving adjuvant therapy

$n = 3$) or the respiratory system ($n = 7$; e.g. pleural effusion $n = 4$). Another major complication was intra-abdominal abscess formation ($n = 7$; e.g. subphrenic abscess $n = 4$). Reoperation was required in four patients: thoracocentesis was needed in two patients with right pleural effusion; the other two had a subhepatic or a subphrenic abscess requiring surgical drainage. Two patients died within 1 month of the second liver resection and were regarded as postoperative deaths. The causes were myocardial infarction occurring on the fourth day after right trisegmentectomy[17], and tonsillar herniation due to an undetected cerebral metastasis[19]. Another (possibly third) patient was reported to be succumbing because of acute bilateral nosocomial pneumonia in spite of aggressive treatment, although the underlying type of cancer was not specified[23]. After excluding this last report, the estimated operative mortality rate was 1·2 per cent (two of 163 patients).

Five reports[12,14,15,17,20] mentioned the use of adjuvant therapy after the second resection for colorectal metastases (*Table 5*). Twenty-nine (45 per cent) of 65 patients received some form of adjuvant therapy, systemic chemotherapy accounting for more than 50 per cent of the cases. Treatment for recurrence after the second hepatic resection is evidently rare enough to be left unmentioned except in a few studies[11,21].

In 48 of 111 patients (43 per cent), resection of the primary colorectal cancer and the hepatic metastases took place at the same operative intervention. These metastases were considered synchronous. In 63 patients (57 per cent), metachronous metastases were removed after a median delay of 13 months after the colorectal resection. The median interval between the first and second liver resection for colorectal metastases was 12 months; there was no difference between synchronous and metachronous disease. The median interval between the second and third liver resection (data obtained from seven patients) was 14 months.

Altogether the ten patients subjected to a third liver resection because of colorectal liver metastases achieved a median survival afterwards of 27 months. A total of 191 second liver resections resulted in a median survival of 30 months; the corresponding 1-, 3- and 5-year survival rates after the second resection were 87, 40 and 26 per cent respectively (*Fig. 3*). Median survival after the first liver resection was 50 months (data obtained from 146 patients) and respective 1-, 3- and 5-year survival rates were 98, 68 and 39 per cent. Median survival after the primary colorectal resection was 68 months (data from 111 patients) and 3-, 5- and 10-year survival rates were 77, 57 and 20 per cent respectively. The 12 patients subjected to additional metastatic surgery beyond the second liver resection achieved a median survival of 34 months.

Table 6 summarizes potential predictors of outcome for patients with colorectal cancer during the course of their disease. Sex and age did not prove prognostically important, and increasing age did not negatively influence survival. Patients above the age of 60 years tended to show a better survival than younger patients, both after the primary colorectal resection ($P = 0{\cdot}07$) and after the first liver resection ($P = 0{\cdot}08$), although these differences did not reach statistical significance. This tendency was, however, not demonstrable when comparing patients above *versus* below 65 years of age.

Survival after the primary colorectal resection was not apparently influenced by the site or Dukes stage of the primary cancer. The appearance in time of the liver metastases did not prove to be of prognostic importance after the first or second liver resection, but it affected survival after the primary colorectal resection, which was shorter in patients with synchronous metastases ($P = 0{\cdot}04$). This is also true for the interval between the hepatectomies. Patients with colorectal disease and an interval longer than 1 year did significantly better than those with a shorter interval, both after primary colorectal resection ($P = 0{\cdot}004$) and after first hepatic resection ($P < 0{\cdot}001$). However, survival after second resection was not apparently influenced by the preceding time interval between liver resections. A comparison between patients

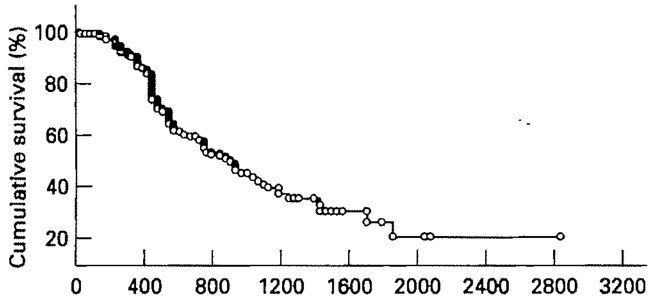

Fig. 3 Survival after second liver resection for recurrent colorectal liver metastases

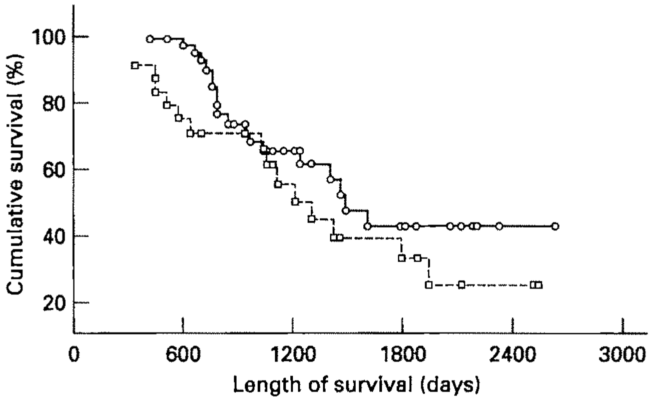

Fig. 4 Survival after first liver resection according to the total number of colorectal metastases (○, fewer than four; □, four or more) resected at first and second liver resection ($P = 0{\cdot}10$, Kaplan–Meier test)

Table 6 Features possibly affecting survival after the primary colorectal procedure and after first and second liver resection for colorectal metastases

	After primary procedure		After first liver resection		After second liver resection	
	No.	P*	No.	P*	No.	P*
Sex						
M	59	0·26	64	0·40	64	0·49
F	42		44		44	
Age (years)						
≤ 60	58	0·07	60	0·08	60	0·23
> 60	43		48		48	
≤ 65	82	0·40	87	0·44	87	0·25
> 65 years	19		21		21	
Site of primary tumour						
Colon	72	0·34	79	0·49	79	0·33
Rectum	27		35		35	
Dukes stage						
B	26	0·18	29	0·43	29	0·09
C	41		44		44	
Timing of first metastases						
Synchronous	48	0·04	48	0·39	56	0·48
Metachronous	63		63		64	
Interval between first and second live resection (years)						
≤ 1	59	0·004	71	0·00007	71	0·14
> 1	52		75		75	
Total number of nodes resected						
1–3	37	0·24	44	0·10	44	0·13
> 3	23		24		24	
Adjuvant therapy after second resection						
Yes					20	0·37
No					24	

*Log rank test

with a total of three or fewer and four or more metastases, removed at the two liver resections, demonstrated that a limited cumulated number of metastases tended to correlate with a longer survival after the first liver resection, although this did not reach statistical significance (P = 0·10; *Fig. 4*). The use of adjuvant therapy did not seem to improve the results of the second liver resection for colorectal metastases.

Hepatocellular carcinoma

The majority of the 128 patients with HCC had concomitant liver disease. In three Asian studies[35,39,45], reporting on a total of 43 patients, the presence of underlying cirrhosis varied between 89 and 100 per cent. In three European studies[33,34,44] HCC was associated with chronic hepatic disease in 57 per cent (ten patients with cirrhosis, two with chronic hepatitis and one with haemochromatosis). Except for one patient with Child grade C hepatic dysfunction, who was alive without disease 6 months after second liver resection[39], no other patient was identified as having poor liver reserve at the time of second liver resection. Another seven patients without concomitant liver disease were identified[33,45]; three of them died with liver tumour 85, 27 and 11 months after second resection. One patient was alive with disease at 47 months and the final three patients were tumour free at 54, 28 and 2 months.

Recurrence of HCC limited to the liver alone after a first liver resection varied between 72 and 91 per cent and was followed by a repeat resection with curative intent in 12–24 per cent (*Table 1*). These repeated resections correspond to 4–14 per cent of all curative liver resections performed (*Table 2*). Data on the extent of resection were recorded from 121 patients[16,33–37,39–43,45,46] (*Table 3*). Some 41 (33 per cent) lobar, 31 (25 per cent) segmental, and 52 (42 per cent) subsegmental resections were performed at the first intervention. Six (5 per cent) lobar, 30 (24 per cent) segmental, and 87 (71 per cent) subsegmental resections were performed at the second liver resection. The calculated morbidity rate after the second resection for HCC was 13 per cent (*Table 4*). Three patients died within 1 month after the operation, one because of bleeding from oesophageal varices secondary to cirrhosis and one from septic complications. The cause of death in the third is not known. The resulting operative mortality rate was 2·3 per cent (three of 128 patients).

The use of postoperative adjuvant therapy after the second resection of HCC was rarely mentioned. One study reported that 17 patients were routinely given adjuvant chemotherapy for 3 days after second liver resection[37]. No postoperative chemotherapy was given to four patients in a comparative study[41]. Non-surgical treatment for recurrence of HCC after second liver resection was known to be applied in nine of 13 patients (five had chemotherapy, four percutaneous ethanol injection and three transcatheter arterial embolization)[39,45]. A number of patients with recurrence received lipiodolization[46].

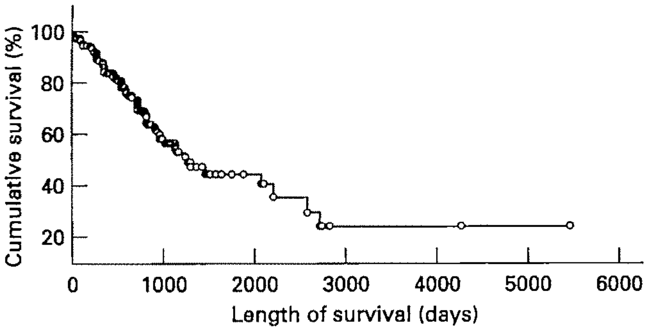

Fig. 5 Survival after second liver resection for recurrent hepatocellular carcinoma

In patients with HCC the median intervals between first and second, and between second and third, liver resection were 19 and 15 months respectively. Median survival times after first (data obtained from 124 patients), second (data from 128 patients) and third liver resection (data from ten patients) were 77, 40 and 29 months respectively. Three-, 5- and 10-year survival rates after first liver resection were 82, 64 and 30 per cent respectively, and the respective 1-, 3- and 5-year survival rates after second resection for HCC were 82, 56 and 40 per cent (*Fig. 5*). If the first surgical intervention is considered as the onset of disease in both colorectal carcinoma and HCC, the latter

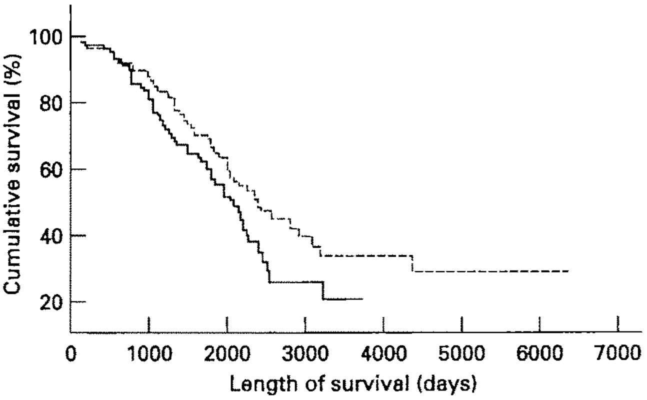

Fig. 6 Survival after primary resection for colorectal cancer (———) and after the first resection for hepatocellular carcinoma (HCC) (- - -). HCC is associated with significantly better survival (P = 0·03, Kaplan–Meier test)

Table 7 Features possibly affecting survival after first and second liver resection for hepatocellular carcinoma

	After first liver resection		After second liver resection	
	No.	P^*	No.	P^*
Sex				
M	70	0·16	79	0·18
F	15		16	
Age (years)				
≤ 50	31	0·20	38	0·25
> 50	72		75	
≤ 65	82	0·31	92	0·43
> 65	21		21	
Interval between first and second liver resection (years)				
≤ 1	33	0·001	33	0·21
> 1	91		91	
≤ 2	71	0·001	71	0·30
> 2	53		53	
Maximal node size at second resection (mm)				
≤ 40			43	0·36
> 40			15	

*Log rank test

appears to have a significantly better prognosis ($P = 0{\cdot}03$; *Fig. 6*).

Several factors were analysed for their possible effect on outcome (*Table 7*). Sex, age and maximal tumour size at second liver resection were not of prognostic importance. Similar to colorectal metastases, for HCC a longer interval between liver resections was related to an improved survival after first resection ($P = 0{\cdot}001$), although this did not affect survival after second resection.

Discussion

Colorectal carcinoma

Recurrence after a first liver resection for colorectal metastases occurs in the majority of patients. The 2-year recurrence rate has been estimated as 50–70 per cent[6,49,50]. Approximately one-third of patients will have recurrence isolated to the liver alone[1,2,51,52]; in the present study this varied between 33 and 48 per cent. Metastatic disease confined to the liver was resected in 15–33 per cent of instances, in comparison to a previously reported rate of 24 per cent[53]. Thus, a second liver resection for colorectal metastases could only be performed in a minority of patients with recurrence after a first hepatectomy. Morbidity and mortality rates of 27·4 per cent and 1·2 per cent respectively were identified, levels similar to those observed after a first liver resection[1,3]. Similar rates were recently published in two multicentre reports of large numbers of reresections for colorectal metastases[53,54], which confirms that reresection may be performed in selected patients in reasonable safety.

Comparing survival after a single hepatic resection with survival after a second hepatic resection may reveal if reresection is worthwhile. A 5-year survival rate of 26 per cent after a second resection for colorectal metastases compares well with the 25–35 per cent reported in patients with only one liver resection[1–3]. Also the aforementioned two recent multi-institutional studies provide similar data on survival[53,54]. Survival after first resection is improved by a subsequent second resection. Patients with colorectal liver metastases and repeated liver resection in the present review had a 5-year survival rate after first liver resection of 39 per cent.

In ten patients the median interval before and the median survival after the third liver resection (14 and 27 months respectively) were similar to those noted at 191 second resections (12 and 30 months respectively). Nordlinger *et al.*[53] also reported on 12 patients who underwent a third liver resection for colorectal metastases with a mean interval before the third liver resection of 15·2 months and a mean survival of 12·5 months. As no effective alternative treatment seems available, and since resection can be performed with reasonable operative morbidity and mortality rates (with a demonstrable effect on survival which in the present study approached survival obtained after a second resection), a third liver resection seems justified in selected patients. Surgery should be considered when feasible, but the actual benefit in survival terms remains unclear. A prospective, randomized study would be needed for a proper assessment.

To improve results it is necessary to identify prognostic factors. Apart from synchronous or metachronous dissemination and the time interval between liver resections, none of the other factors studied proved statistically significant. No feature predicted survival after second hepatectomy. Patients with colorectal liver cancer in the older age groups demonstrated a survival similar to that of younger patients. Patients above the age of 60 years tended to do better than younger patients, both after the primary colorectal resection ($P = 0{\cdot}07$) and after the first liver resection for metastases ($P = 0{\cdot}08$). A similar beneficial effect on survival after a first liver resection for colorectal metastases, favouring patients older than 60 years, has been reported previously[55]. These results may be attributed to the use of stricter selection criteria for older patients. In the elderly, factors other than age, such as performance status, co-existent heart disease, dementia, diabetes, are considered when evaluating surgical risks and benefits[56]. It may therefore be expected that resectability rates are lower in the elderly, rendering morbidity, mortality and survival rates after liver resection comparable to those of younger patients[1,56,57].

The present review suggests that the primary site of the cancer, whether colon or rectum, has no prognostic importance[1,32,51,58]. Concerning stage of the primary tumour, opinions differ about whether patients with metastases from Dukes C colorectal carcinoma do better[24,51] or not[32,59,60] after liver resection than those with metastases from Dukes B tumours. The present review does not demonstrate a significant decrease in survival in patients with Dukes C carcinoma.

The influence of synchronous *versus* metachronous metastases on survival after liver resection has been discussed. Several studies have failed to show any difference in survival[24,32,51], while others have found synchronous metastases to be associated with a less favourable outcome[58,61]. In a review, Ballantyne and Quin[3] estimated the 5-year survival rate after resection for metachronous lesions to be somewhat better (31 per cent) than that after resection for synchronous disease (27 per cent). In the present study, patients with metachronous metastases did no better after either the first or the second hepatic resection, but survival after the primary colorectal resection was considerably improved compared with that for patients with synchronous metastases.

Patients with a disease-free interval exceeding 1 year after the colorectal resection have been said to have a significantly improved survival after liver resection, compared with patients with an interval of less than 1 year[59]. It has been proposed that a long interval may indicate a biologically less aggressive tumour[60]. The interval between first and second liver resection has also been studied. An interval exceeding 1 year correlated with significantly better survival after primary colorectal resection and after first liver resection. A longer interval tended to correlate with increased survival after second liver resection, although this was not statistically significant. Recently, a multi-institutional study failed to demonstrate a significant difference in survival after repeated liver resection between patients with a disease-free interval after the first liver resection of less than 1 year and those with a disease-free interval of more than 1 year[54]. It may be that subclinical disease is present in a number of patients after the first liver resection, who would therefore benefit from repeated liver resection after a short interval.

It has been suggested that a limited number of metastases at the first liver resection correlates with a better prognosis[51,55,59]. In the present study, the total number of metastases resected at the two liver resections tended to influence outcome after first liver resection, but not significantly. Others have reported that the number of metastases resected at second resection does not significantly influence long-term survival, although a higher number of nodes (more than three) results in a higher mortality rate during the first year after operation[54].

The use of adjuvant therapy after second liver resection did not result in improved survival. However, some studies on adjuvant chemotherapy after a first liver resection have appeared and further investigations are needed[62,63]. Also, for patients with irresectable metastases, attempts have been made to prolong survival and maintain quality of life, mainly by regional chemotherapy[64,65]. Transplantation would be a treatment option for disease restricted to the liver. Such a patient, excluded from analysis, underwent an orthotopic liver transplantation 25 months after the first (palliative) liver resection, but died shortly after the operation[12]. Although the spectrum of diseases treated by liver transplantation has broadened in recent years, there is a growing reluctance about regarding malignant disease as an indication because of the high risk of tumour recurrence[66], which may be particularly high in patients with cancer of colorectal origin. However, it should be stated that possibly one-third of patients with recurrent disease after a first liver resection may have disease limited to the liver[1,2,51,52]. These patients, usually characterized by adequate liver function but poor prognosis, may be candidates for future liver transplantation.

Factors reported predictive for outcome after first liver resection for colorectal metastases include free resectional margin, unilateral or bilateral disease, and presence or absence of regional lymph node metastases and extrahepatic disease[2,3]. In the present review, 12 patients were identified who had removal of localized extrahepatic disease in addition to a second resection for colorectal metastases. The median survival in these patients was 34 months, which is 4 months longer than that for the total series of patients.

Hepatocellular carcinoma

Recurrence of HCC occurs in 43–57 per cent of patients within 2 years of first tumour removal[9,42,67], a rate lower than that for colorectal metastases. Disease confined to the liver alone is present in a higher percentage in HCC, in the present study varying between 72 and 91 per cent, which is similar to other reports[9,10,51,67]. Resectability varies between 12 and 24 per cent, from which it follows that only a few patients are selected for a second surgical intervention. After second resection complications occur in 13 per cent of patients and reoperation is rare, which compares well with morbidity rates observed after first resection[42,44]. This, together with a mortality rate of 2·3 per cent, suggests that second and even third resections of the liver are well tolerated in selected patients.

The value of a repeated liver resection for HCC can be expressed as prolonged survival. A 5-year survival rate of 30–50 per cent after a single liver resection[5,7–10] is similar to 40 per cent after a second resection. In these patients the 5-year survival rate after the first of the two resections was calculated as 63 per cent in the present study. Partially responsible for this result are the ten patients who received an additional third liver resection. The disease-free interval before and survival after third resection were shorter than before and after second resection.

Identification of factors influencing survival may be useful. Neither sex nor age affected survival. Recent reports suggest that the results of liver resection for HCC in the elderly are satisfactory and not necessarily worse than those in younger patients with otherwise similar clinical features[68–70]. A longer interval between hepatectomies predicts an improved total survival ($P = 0{\cdot}001$), but it does not seem to influence survival after the second resection for HCC. Similar findings have been noted in patients with colorectal liver cancer.

The size of the HCC influences the extent of hepatectomy which, in turn, probably affects operative mortality. It is generally believed also to affect long-term prognosis[10], although the present study could not support this with respect to second liver resection. Other factors, such as presence of cirrhosis, vascular invasion, satellite nodes, absence of capsule formation and tumour growth at the resectional margin, have been reported to be associated with a less favourable outcome after first liver resection for HCC[10,67]. It may be that the same factors also affect prognosis after second resection, but this requires further study.

Efforts are frequently made to decrease the risk of recurrence and so potentially to improve the outcome for patients with irresectable HCC. Surgical resection combined with chemotherapy may result in longer disease-free survival, but this needs further evaluation by randomized trials and long-term follow-up[71]. The same is true for more recently introduced therapeutic modalities, such as transcatheter arterial chemoembolization, percutaneous ethanol injection and cryosurgery, which may be applied when surgical intervention is no longer considered feasible[5,71]. Such a situation probably occurred for a patient[34], excluded from the present analysis, who underwent an unsuccessful liver transplantation after a trisegmentectomy and three subsequent wedge resections. Transplantation as a potential therapy for HCC still carries the risk of early tumour recurrence, despite excluding patients with extrahepatic malignancy. In general, the indications for liver transplantation are moving away from malignant, in favour of benign, disease[66]. At the same time, however, it is recognized that carefully selected patients with HCC (small and uninodular or binodular tumours, cirrhosis, poor liver reserve) benefit more from liver replacement than from liver resection, leaving a definite but incompletely defined role for liver transplantation in the treatment of HCC[72,73].

In conclusion, repeated liver resection may be performed without major risk in a selected group of patients with recurrence of colorectal liver metastases or HCC. This offers a hope of long-term survival. To improve the results of resectional therapy for liver cancer, more effort should be made to ensure early detection and careful follow-up. Selection criteria for resectional operations on the liver require further definition.

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British Journal of Surgery 1996, 83, 902–909

Review

Stapling instruments for intestinal anastomosis in colorectal surgery

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The circular stapling instrument has had a major impact in the practice of colorectal surgery. Stapling technology was pioneered in the early part of this century and subsequently modified. Russian initiatives led to development of the original circular stapling instrument and further progress has resulted in instruments that are widely available, reliable and totally disposable. Mechanical failure is now rare and malfunction is generally due to operator error. Complications related to the stapling technique are uncommon, although anastomotic stricture may be more frequent than when handsewn anastomosis is performed. A stapling instrument facilitates and may expedite a surgical procedure but it is an adjunct to, and not a substitute for, meticulous surgical technique.

The restoration of intestinal continuity after resection of a portion of the gastrointestinal tract is a routine surgical procedure. The concept of mechanical devices to facilitate intestinal anastomosis is as old as the surgery itself. Much of the original enthusiasm[1–3] centred on intraluminal devices, such as the Denans ring in 1826 and Murphy's anastomosis button in 1892. The ideas were based on intestinal suturing. Antoine Lembert[4] had proposed serosa-to-serosa apposition as the fundamental basis of successful intestinal suture in 1826 and many of the stapling instruments use this principle. The concepts and techniques of intestinal stapling have been developed only in the present century and major advances can be broadly categorized into three time phases.

The three phases comprise the pioneering work of Hultl in the early part of this century, the persistence of the Russians in developing stapling technology, and subsequent American adaptations to provide reliable, disposable equipment, thereby making stapling widely available. Some of the important developments are reviewed and the principles, as they relate to the current practice of colorectal surgery, are outlined. The term 'stapling gun' is used interchangeably with 'stapling instrument'. Where possible, comparisons between suturing and stapling are reviewed with regard to advantages of one technique over the other, immediate and delayed complication rates and cost.

Hultl and the first modern stapling instrument

Humer Hultl[5] produced the first sophisticated stapling instrument in Budapest in 1908. Many of the original principles have stood the test of time and are still used today, including the use of fine metal staples, placement of a double row of staples on each side, and closure of the staples in the B configuration. Hultl also recognized the importance of two phases in intestinal stapling: initial fixation of the tissue by appropriate crushing followed by a mechanism to drive home and close the staples.

The Hultl stapling instrument was used in 1908 for gastrectomy; the patient survived[5]. However, the instrument was cumbersome to assemble and weighed 3·5 kg. For this reason several modifications occurred, the most renowned being that of von Petz[6,7]. A significant modification was described by Friedrich[8] in 1934: the invention of removable cartridges that could be preloaded, allowing multiple use at one operation. One of the first references to use of a stapler specifically in colorectal surgery was at this time, when von Seemen[9] of the University Clinic in Munich reported experience with an L shaped stapler for sacral amputation of rectal cancer.

Russian initiatives

During World War II a programme was initiated by the Scientific Research Institute for Experimental Apparatus and Instruments in Moscow. The design brief was that 'the mechanical suturing apparatus should allow a biological result superior to that of manual suturing, be independent of the skill of the surgeon, and cause less trauma than a manual technique'[2,10]. Some of the first instruments produced were those of Gudov in 1950 and later Androsov[11] for vascular anastomosis. The techniques used and the instruments required long segments of normal vessel and were highly complex. Indeed little further progress has been made to this day in the field of vascular anastomotic stapling guns. A second basic type of Russian instrument[12] was one that approximated, stapled and cut; this was the forerunner of the current GIA (Auto-suture, Ascot, UK) and the Linear Cutter LC (Ethicon, Edinburgh, UK).

A major advance was a stapler designed to perform an inverting end-to-end intestinal anastomosis. This was a cylindrical instrument resembling a sigmoidoscope with a nose cone that could be opened away from, and subsequently closed toward, the main cylinder. The proximal and distal bowel were encircled with a purse string and were then drawn over the nose cone and main cylinder to be tied on to the shaft. The nose cone and cylinder were approximated. The gun was then 'fired' by squeezing the handle. A single row of staples was driven home and a circular knife cut out two excision discs or 'doughnuts' of bowel. The design and configuration of this gun lent itself particularly to techniques of peranal colorectal stapling. The modern successor to this circular

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Paper accepted 19 January 1996

stapling instrument has had a great impact on colorectal surgery over the past 20 years.

American modifications

In 1958 Mark Ravitch (1910–1989), while travelling in Russia, observed the 'brilliant use of the staple instruments in pulmonary surgery' and thus began a lifelong career of design modification and clinical evaluation of stapling devices[13,14]. Ravitch and colleagues[13–15] inspected, tested and modified Russian stapling instruments, in particular[16] the circular stapling KTs-25. Ravitch noted mucosal defects arising between individual rows of staples and recommended preloaded, presterilized, disposable cartridges with a staggered staple line and a curved instrument shaft for rectal use. To develop this project, Ravitch began work with Felix Steichen[14] in 1963 and in 1964 a new company, the United States Surgical Corporation (USSC; Norwalk, Connecticut, USA), was formed to develop their staplers. USSC trade in the UK under the name Autosuture. The successful use of the end-to-end circular stapler, with a double row of staggered staples, was reported in 1977 and the totally disposable gun[13,14] in 1978. At around this time the nomenclature of these guns was rationalized by Autosuture into convenient abbreviations, such as GIA (gastrointestinal anastomosis), TA55 (thoracoabdominal, 55 mm) and EEA (end-to-end anastomosis). This nomenclature has been retained with minor modifications for novel developments such as the CEEA (curved end-to-end anastomosis) gun produced in 1987. The curved shaft of this instrument facilitates its passage into the rectum. Further developments have been the detachable anvil (Premium CEEA) and, the most recent modification, a spring-loaded anvil that flips to the horizontal position when fired (Premium Plus CEEA). As Autosuture has retained these descriptive names, competitors must use alternatives for similar instruments; this has resulted in confusion in the minds of surgeons and, indeed, in many publications. Waxman and colleagues[17] have recently addressed this problem and proposed a classification of intestinal stapling devices into two types, namely circular stapling (CS) and linear stapling (LS) instruments. They suggest that linear staplers be further subdivided into vertical linear staplers (VLS) and horizontal linear staplers (HLS). The main stapling gun manufacturers with markets in the UK are Autosuture and Ethicon; *Table 1* outlines their respective instruments. Autosuture have recently bought over an American stapling company called 3M (Minneapolis) and a new range of linear staples will soon be launched.

Table 1 Comparison of intestinal stapling instruments

	Manufacturer	
	Autosuture/ United States Surgical Corporation	Ethicon
Circular		
	Premium CEEA	Proximate ILS
Diameter (mm)	25, 28, 31	21, 25, 29, 33
Vertical linear		
	TA	Proximate LS
Length (mm)	30, 55, 60, 90	30, 60, 90
Flexible	Roticulator	Proximate access
Length (mm)	30, 55	55
Horizontal linear		
	GIA	Proximate PLC
Length (mm)	30, 60, 90	55, 75

CEEA, curved end-to-end anastomosis

There has always been controversy as to whether mucosa-to-mucosa stapling would heal properly. However, everting anastomoses had been shown to heal by Astley Cooper and by Travers[18] in 1812. When bowel is stapled, the compression produces a mucosal wound which then heals[13,14,17].

Stapling *versus* suturing in colorectal surgery

The feasibility of performing anastomosis to the lower rectum or anal canal with the circular stapling gun has always been appealing because of the presence of a natural accessible orifice for insertion of the stapler. The early results from Russia[10,12] stimulated Goligher, among others, to evaluate the circular stapler in this regard. In 1979 Goligher and colleagues[19] reported results of colorectal anastomosis in 62 patients with the Russian model 249 suture gun. They concluded that the gun was at least as good as hand suturing, with fewer clinical or radiological leaks, and that it 'enables an anastomosis to be made at a lower level than would be possible by the conventional suture technique through the abdomen'.

The concept that the circular stapling gun could reduce the number of patients with rectal cancer requiring abdominoperineal resection was popularized in the early 1980s[20,21] and continues to be proposed as one of the main advantages of stapling devices[17]. There were numerous reports in the subsequent decade of personal, mostly favourable, experience using the circular gun; these have been well summarized and analysed by Ravitch, Steichen and others[13,14], and by Waxman and colleagues[17]. The main theoretical advantages attributed to circular stapling devices include lower rate of anastomotic leakage[19–21] and the ability to perform more distal anastomosis[19–22]. Conversely, stapling has been associated with intra-operative technical problems[20] and with anastomotic stricture[23]. There have been a few randomized controlled trials which have directly compared suturing and stapling in colorectal surgery; analysis of some of these trials is worthwhile.

Stapling versus *suturing: randomized controlled trials*

To my knowledge there have been only six completed randomized controlled clinical trials[24–29] that compared stapling with suturing for 'low' colorectal anastomosis. Radiological assessment of the anastomosis was performed in the five most recent trials[25–29]; contrast radiography is the only way of determining the true leakage rate as many leaks do not manifest themselves clinically[30]. The incidence of clinical and radiological leakage is shown in *Table 2*, in which reports are summarized in chronological order.

Beart and Kelly[24] considered 80 patients but conditions in ten were thought to be 'too difficult' for suturing and the anastomoses were stapled; the remaining 70 patients were randomized with one clinical leak in each group. Radiological assessment was not performed. Brennan and colleagues[25] studied 100 patients overall but only 19 had low anterior resection. They concluded that there was no

Table 2 Randomized controlled trials of stapling *versus* suturing in low colorectal anastomosis

		Staples			Sutures		
			No. of leaks			No. of leaks	
Reference	Year	Total	Clinical	Radiological	Total	Clinical	Radiological
Beart and Kelly[24]	1981	35	1	—	35	1	—
Brennan *et al.*[25]	1982	9	2	1	10	4	1
McGinn *et al.*[26]	1985	58	7	14	60	2	4
Everett *et al.*[27]	1986	44	0	7	50	2	6
West of Scotland and Highland Anastomosis Study Group[28]	1991	111	9	5	113	5	13
Fingerhut *et al.*[29]	1994	54	2	4	59	5	6

difference between stapling and suturing but that stapling 'considerably facilitates the performance of a low anterior resection'. Furthermore, the Russian SPTU circular stapling gun was used in this series. Modern circular stapling instruments, with a double-staggered row of staples, are undoubtedly superior and more reliable than the Russian devices. The results of McGinn and colleagues[26] are at variance with the other trials: a clinical and radiological leakage rate of 36 per cent for stapling, compared with 10 per cent for an interrupted extramucosal handsewn technique. There were four technical EEA stapling gun failures, two considered due to operator error and two to mechanical problems. Everett and colleagues[27] looked at left colonic anastomosis and reported no clinical but seven radiological leaks in 44 stapled anastomoses, compared with two clinical and six radiological leaks among 50 sutured anastomoses. They noted that the mean operating time was significantly less for stapled anastomosis. However, it is not possible to assess from this paper how many anastomoses were 'low' colorectal, which are those at greatest risk of leakage.

The largest study has been from the West of Scotland and Highland Anastomosis Study Group[28]. The investigators randomized all reconstructive anastomoses after colonic or rectal resection. They concluded, taking the whole series of 1004 patients randomized, that 'the incidence of clinical leakage was similar between the two groups (sutured 3·2 per cent, stapled 4·7 per cent), while for radiological leaks (in those anastomoses assessed radiologically) the incidence was significantly higher in the sutured group (12·2 per cent *versus* 4 per cent $P < 0·05$)'. Considering low colorectal anastomosis (111 stapled, 113 sutured), the differences persist, although the rate of clinical leakage appears higher (albeit not significantly) with stapling. Another conclusion from this study was that 'stapling instruments afforded significantly quicker anastomoses, mean(s.e.m.) 28·1(0·07) *versus* 14·3(0·05) min ($P < 0·001$) and quicker operations, mean(s.e.m.) 115·5(2·4) *versus* 103·8(2·2) min ($P < 0·001$)'. The investigators agreed that stapling is more expensive than suturing but 'when analysed in the context of total cost of patient care, stapling instruments constitute approximately 5 per cent of the total expense of the entire hospital admission'[28].

The study reported by Fingerhut and colleagues[29] on behalf of the French Association for Surgical Research randomized 113 patients and concluded that 'fewer anastomotic leaks occurred in the stapled group (11 *versus* seven)'. Nevertheless, there were nine mishaps with the stapler and significantly more strictures in this group at 8 months (eight of 50 *versus* two of 52). The overall conclusion of the study was that suturing and stapling were equally appropriate with no evidence that the stapling gun allows more distal anastomosis, although stapling was faster. Interestingly, in a parallel study, the same group of investigators[31] reported the only large randomized study of linear stapler reconstruction compared with four different hand-suturing techniques for ileocolonic anastomosis after right hemicolectomy for cancer. Again, all patients underwent routine radiological assessment of the anastomosis for the purposes of the study. There were fewer clinical and radiological anastomotic leaks after stapling, three of 106 (2·8 per cent) compared with 28 of 334 (8·4 per cent) in the combined hand-sutured group. The authors concluded that 'in spite of the fact that staples are approximately ten times more expensive, our results suggest performing side to side (GIA + TA) mechanical anastomosis after right colon resection for carcinoma'.

Overall conclusions from randomized controlled studies

It appears that colorectal anastomotic stapling is faster than hand suturing, but it is more expensive. The overall trend is toward a reduction in leakage rate. Surprisingly, the reduction in leakage rate has been noted more for ileocolonic anastomosis after right hemicolectomy[31] and for all gastrointestinal anastomoses[28] rather than for the more technically difficult colorectal anastomosis. The problem of mortality and morbidity of leakage from colonic anastomosis is considerable, and may more than compensate for the increased cost associated with the use of stapling guns, provided that the leakage rate can be reduced by stapling.

Leakage rate in non-randomized studies

Waxman and colleagues[17] reviewed the leakage rate in 43 studies totalling 3501 anastomoses with a circular stapler and two purse-string sutures. These studies were mainly non-randomized and the average clinical leak rate was 7 per cent. In a previous review in 1983 Waxman[32] reported that the combined leakage rate (clinical and radiological) in 14 studies in which the radiological rate was assessed was 81 of 509 (16 per cent). He concluded that the standard to which all other techniques should be compared was the single-layer extramucosal technique described by Matheson and Irving[33], with one radiological leak in 15 colorectal anastomoses below the peritoneal reflection. While Matheson's results are indeed excellent, this was a small series and might not apply to surgeons in general.

One of the main predisposing factors influencing leakage rate appears to be the height of the anastomosis from the anal verge, with the lowest anastomoses having the greatest risks[17,21]. Heald and Leicester[21] recorded 13 clinical and four radiological leaks and noted that all these occurred at anastomoses below 7 cm. Indeed, they noted a combined leak rate in this group of 23 per cent and, therefore, advocated temporary colostomy in all patients undergoing low anterior resection. While Heald continues to advocate temporary defunctioning[34], others disagree[35,36]. A selective approach to defunctioning the low anastomosis is often adopted[36], although it is not possible to predict all potential leaks[35,36].

An interesting recent report of a randomized study assessing the use of a colonic J pouch following low anterior resection noted that the leak rate was significantly lower after construction of a colonic J pouch compared with straight colonic anastomosis[37].

Mechanical failure of circular staplers

Most series in which stapling instruments have been used for colorectal anastomosis report complications directly attributable to gun malfunction. The recorded malfunction rates, where stated, in randomized controlled trials are shown in *Table 3*. In many instances this was due to operator error, although mechanical failure of the instrument accounted for a substantial proportion. This is hardly surprising and, despite technical innovations and improvement in stapling gun design, it seems likely that an occasional mechanical failure will continue to occur. Some of the failures may well be due to variation in the thickness of the bowel wall. If the bowel is too thin or too thick, stapling may not be appropriate and suturing should be performed.

Table 3 Randomized controlled trials of stapling *versus* suturing: stapling gun failure and anastomotic stenosis rates

	Stapling gun failure		Stenosis	
Reference	Operator	Mechanical	Staples	Sutures
Brennan *et al.*[25]	2 of 50	1 of 50	0	0
McGinn *et al.*[26]	2 of 58	2 of 58	Not stated	
Fingerhut *et al.*[29]	9 of 54	—	8 of 50	2 of 52

The survey of the American Society of Colon and Rectal Surgeons (ASCRS), published[38] in 1981, reported technical problems in approximately 5 per cent of 3594 operations performed by 243 surgeons. Complications due to operator error may have decreased due to improvements in stapling gun design, but stapling should be performed only by someone trained in and familiar with both manual and stapled anastomoses.

Anastomotic stenosis

Of all colonic anastomoses, those deep in the pelvis involving the low rectum or anal canal have a particular propensity to become stenosed. While stenosis may occur whatever technique is used, it has been suggested that it is more frequent after stapling; some of the randomized studies support this[29]. Waxman[32] reviewed stenosis rates in 20 studies up to 1983 and found that 53 of 827 stapled anastomoses (6 per cent) were stenosed. Similar rates were reported in the ASCRS survey[38] with stenosis in 352 of 3594 cases (10 per cent). However, most stenoses are minor and usually asymptomatic; they may be dilated endoscopically. Heald and Leicester[21] proposed that 'permanent stricturing occurs only as a result of failure of healing by first intention with granulation tissue formation and consequent fibrosis', an idea supported by Ravitch and colleagues[14]. In a recent update, Waxman *et al.*[17] stated that the mean reported anastomotic stenosis rate was 8 per cent in 33 studies of 2680 single-stapled circular anastomoses. They noted that stenosis appears more frequently following use of a double row of staples compared with the single row of the old Russian guns. Waxman and colleagues[17] hypothesize that the ideal circular stapler should apply one row of absorbable staples with a large luminal diameter. Even though luminal diameter does not appear to be a major factor in the incidence of stenosis following use of a circular stapler[17], it seems sensible to use the largest possible lumen size when constructing any anastomosis.

Recurrence of colorectal cancer after sutured and stapled anastomoses

Concern has been expressed regarding the possibility of an increase in cancer recurrence rate, particularly for local recurrence, in patients having restoration of colonic continuity with stapling guns. Recurrence rates of 20–32 per cent have been reported[39–43] after restorative resection for rectal cancer, with the suggestion that the increasing use of stapling instruments resulted in an inappropriate abandonment of abdominoperineal resection. Anderberg *et al.*[40] proposed that stapling guns facilitated lower anastomoses, thereby compromising tumour clearance.

Other mechanisms have been proposed whereby stapling instruments might influence the recurrence rate, in particular the scraping of tumour cells by the intraluminal stapling gun and their deposition at the anastomosis[43]. In this context it is of interest that one of the highest recorded recurrence rates of 32 per cent[39] occurred in a series in which the authors specified that they did not irrigate the rectal stump before introduction of the circular stapler. However, others have failed to identify an adverse effect associated with stapling[44,45]; one of the lowest local recurrence rates described is in a personal series by Heald and colleagues[34] in which the circular stapling gun was used for all anastomoses. A recent authoritative review of the literature concluded that use of stapling guns *per se* does not influence the local recurrence rate[46]. The main factor in reduction of local recurrence seems to be surgical technique, with total mesorectal excision as standard treatment for all middle and low rectal cancers[34,46].

It has been hypothesized that the type of material used to anastomose the colon might influence recurrence. Phillips and Cook[47] suggested that steel wire resulted in a significantly higher incidence of anastomotic tumours, compared with silk, in experimentally induced colonic cancer in rats. McGregor and colleagues[48] examined the adherence properties of rat colonic cancer cells to various suture materials, including monofilament polypropylene, monofilament stainless steel wire, braided polyglycolic acid and braided polyamide. They also studied the transfer of malignant cells from the lumen into the suture track; tumour adherence and transfer were less with monofilament sutures (and least with stainless steel), compared with braided materials. McGregor *et al.*[48] suggested that stainless steel (in the form of staples) was associated with the lowest cancer recurrence rates. In support of this Uff and colleagues[49] recently reported that free-lying malignant cells had the highest tendency to adhere to protein-based and multifilament materials, with least adherence to monofilament steel. The results of these studies confirm that wire staples do not appear to increase, and may even decrease, the local cancer recurrence rate. Whatever method is used, the bowel lumen should be cleansed before anastomosis, and washout of the rectal stump with a cytocidal solution may be particularly important before restoration of intestinal continuity by stapling[34,50].

The results of the West of Scotland randomized controlled trial examining the recurrence of colorectal cancer after sutured and stapled large bowel anastomosis are interesting[51]. In all, 294 patients undergoing potentially curative resection for colorectal cancer were randomly allocated to have sutured ($n = 142$) or stapled ($n = 152$) anastomosis. The mean(s.e.m.) incidence of tumour recurrence at 24 months follow-up was 29·4(4·4) per cent after suturing and 19·1(3·9) per cent after stapling ($P < 0{\cdot}05$). The corresponding rates for cancer-specific mortality at 24 months were 22·3(4·1) and 10·9(3·0) per cent respectively ($P < 0{\cdot}01$). The investigators concluded: 'these results suggest that in colorectal cancer surgery the use of stapling instruments for anastomotic construction could be associated with a reduction in the incidence of recurrence and mortality rate by as much as 50 per cent'.

It is difficult to explain such a large difference in outcome and the authors[51] have made the following suggestion. They cited their previous demonstration that sutured colorectal anastomoses have a higher incidence of radiological leakage compared with stapled anastomoses[28], and that clinical or subclinical anastomotic leaks might be associated with a higher incidence of tumour recurrence[52]. The clinical leak rate was similar in their two randomized groups[51], but the majority did not have contrast radiological assessment of the anastomosis. However, they hypothesized that the radiological leak rate might be higher after suturing and that this might influence cancer recurrence. This argument is tenuous and the benefit attributable to stapling in this randomized study remains to be adequately explained.

Ileoanal pouch surgery

Restorative proctocolectomy with ileal reservoir formation and ileoanal anastomosis has become an alternative to proctocolectomy and terminal ileostomy for patients with ulcerative colitis, familial adenomatous polyposis and some forms of functional bowel disease[53]. The original technique involved a difficult ileoanal handsewn anastomosis[53]. Heald and Allen[54] proposed that the circular stapler could be used for the ileoanal anastomosis, after noting that several of their patients undergoing low anterior resection for rectal cancer had squamous epithelium in the lower 'doughnut'. They described the technique of circular stapled ileoanal pouch formation in 1986, using a manually inserted distal purse string. Subsequently, techniques were described for totally stapled abdominal restorative proctocolectomy with a J pouch; a particularly elegant description was given by Kmiot and Keighley[55] in 1989. Many investigators have found that stapled ileoanal pouch construction is faster and safer than hand suturing[56]. Indeed, Wettergren and colleagues[56] reported that the median duration of the handsewn operations was 270 min compared with 197 min for stapled pouches ($P < 0{\cdot}001$). Surprisingly, they also found that the incidence of anastomotic stenosis was 23 per cent with handsewn and 6 per cent with stapled pouches ($P < 0{\cdot}02$). However, this was a retrospective study.

Seow-Choen and colleagues[57] performed a randomized study comparing handsewn with stapled ileoanal pouch anastomosis. They reported no significant difference in the complication rate or functional outcome in 32 patients; a further small randomized study came to similar conclusions[58]. Both groups concluded that handsewn ileoanal anastomosis was better due to complete excision of the rectal mucosa. In summary, it appears that sutured ileoanal anastomosis, in the hands of experts, is as effective as stapled anastomosis, but that stapling guns significantly reduce the operating time, particularly if a totally stapled pouch is performed.

Double stapling in low anterior resection

The original circular stapling technique for colorectal anastomosis[13,14] involved insertion of a purse string in the cut edge of the rectum or anal canal. In 1980 Knight and Griffen[59] described a double-stapling technique in which the rectum is cross-stapled with a linear stapler before peranal introduction of the circular stapler. The theoretical risk of anastomotic failure at intersecting staple lines has been disproved by studies in dogs by Julian and Ravitch[60]. There are now a number of reports attesting to the feasibility and safety of the technique[50,61–64]. Some[50] have used only a horizontal linear stapling instrument (Autosuture TA55) while others[64] use the more expensive flexible stapler (Autosuture Roticulator).

To the author's knowledge only a single randomized study has been published comparing single- and double-stapling circular anastomosis[65]. In this study 70 patients were randomized to single or double stapling. There was no significant difference but there was a trend toward less leakage after double stapling (one of 35 clinical and two of 35 radiological leaks for double stapling *versus* three of 35 and five of 35 respectively for single stapling). Controversy continues about the relative safety of double stapling, although the technique is now widely used in preference to insertion of a distal manual purse string for colorectal anastomosis[17]. Nevertheless, a manual purse string is still occasionally necessary after resection of a very low tumour and it may require to be inserted peranally.

Similarly, many surgeons currently use a double-stapling technique in the construction of an ileoanal pouch[55], although the technique does not result in as radical a clearance of the rectal mucosa as does mucosal proctectomy[57,58]. A technique of everting the rectal stump through the anal canal and cross-stapling the anal canal externally has been described[66]. The tissue distal to the linear stapler is excised and the anal stump is then inverted to its normal position. This facilitates insertion of the linear staple line and usually results in more extensive excision of the rectal mucosa than is possible with an abdominal linear stapler. However, eversion may have a detrimental effect on sphincter function. A recent study suggested that anorectal eversion impairs the motor and sensory functions of the anal sphincter, compared with preoperative measurements in the same patients[67]. However, these investigators assessed only patients who had restorative proctocolectomy by an eversion technique and found that most achieved satisfactory continence despite these physiological changes. They concluded that, based on previous studies[68–70], the clinical outcome of restorative proctocolectomy by the eversion technique is better than that of mucosectomy and endoanal anastomosis, but not as good as the outcome following stapled end-to-end anastomosis without eversion. They recommend that, if end-to-end anastomosis is technically very difficult (for example in a male patient with a narrow pelvis), eversion is preferable to mucosectomy and endoanal anastomosis in terms of postoperative function.

Side-to-end anastomosis in anterior resection

A useful modification of the circular stapling technique of colorectal anastomosis was described in 1980 by Adloff and colleagues[71]. In this technique the circular gun is passed into the open end of the proximal colon (or through a colotomy proximal to the pathology). The shaft, or spike in the modern instrument, is then passed out through the antimesenteric wall of the proximal colon. The head of the instrument is placed in the rectum from above and a purse-string suture inserted around the edge of the rectum and tied. The head is then connected to the shaft, and the gun closed and fired from within the abdomen. The anastomosis can be inspected through the open end of the proximal colon, before closure by linear stapler or manual suturing. They recommend this modification when a discrepancy in size exists between the rectum and a large-calibre proximal colon, encountered particularly in large bowel obstruction. Furthermore, it also allows circular stapling when unexpected anterior resection is required and the patient has not been placed in the lithotomy–Trendelenburg position. Care must be taken to ensure that all bowel to be anastomosed has been carefully cleansed with a cytocidal solution before stapling.

Useful techniques

'Triple stapling'

The importance of luminal washout has been stressed by many investigators[34,46,63]. The rectum should be irrigated below an occlusion clamp before stapling. If a double-stapling technique is used it is often difficult to apply the linear stapler below the clamp, especially in a narrow pelvis. A new technique has recently been described[72]. The linear stapler, TA30, 55 or 60 with 4·8-mm staples (Autosuture), or LS30 or 60 (Ethicon), is placed distal to the tumour after full mobilization of the rectum; it is then closed and fired. The stapler is unlocked and removed to leave an occlusive row of staples. The rectum is irrigated and may be inspected if desired. Distal resection can be extended if necessary. A further cartridge is loaded on the TA55, which is then reapplied across the cleansed rectum distal to the proximal occlusion staple line and fired (*Fig. 1*). The rectum is sectioned above the TA55 stapling gun and standard double stapling is then performed.

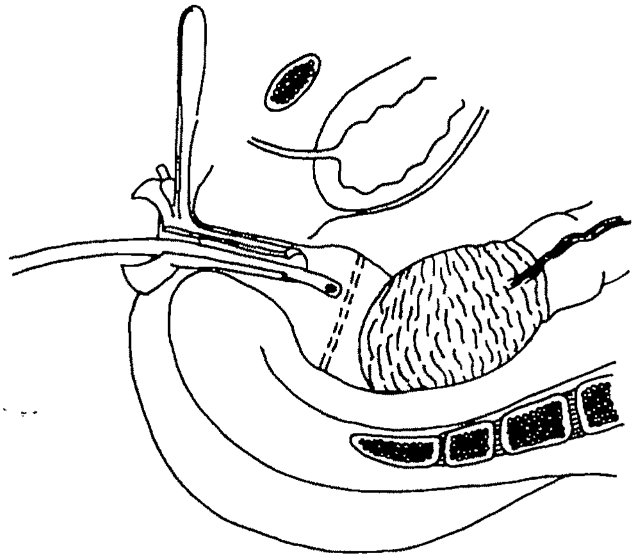

Fig. 1 The rectum has been cross-stapled below the tumour and the rectal stump is irrigated peranally with a cytocidal solution. The cleansed rectal stump is then cross-stapled below the occlusion staple line and the rectum is divided proximal to the distal staple line, before standard double stapling

Excision of recurrent anastomotic stricture

A method of treating anastomotic stricture with the circular gun introduced peranally was reported[73] in 1986. This ingenious technique involves opening of the circular stapler within the bowel across the stricture, which often requires prior dilatation. The gun is then pushed to one side, closed and fired, thereby excising a crescent of the fibrotic ring. A further modification of this technique was reported[74] in 1993; a laparoscopic Endo-GIA device is passed peranally and, under direct vision via a colonoscope, the stricture is divided with the Endo-GIA.

Laparoscopic colonic surgery

The dramatic effects of minimally invasive laparoscopic cholecystectomy have stimulated an interest in laparoscopic colonic surgery[75]. Both horizontal and vertical linear stapling instruments are now available for use via a laparoscope. Many ingenious techniques have been described to facilitate laparoscopic colonic resection. In broad terms the techniques are similar to those used in open surgery; endoscopic staple guns are continually being developed. The exact role of laparoscopic colonic surgery is still uncertain, particularly in relation to cancer; as yet benefits are unproven apart from a cosmetic advantage[75,76]. Early unexplained port-site recurrence is a particular problem[75,76]. While development continues, the current consensus is that laparoscopic colorectal surgery may be contraindicated in patients with potentially curable colorectal cancer[75,76].

Conclusion

Stapling instruments should be regarded as an adjunct to, not a substitute for, meticulous surgical technique. A fundamental principle of intestinal surgery is that it is not possible to staple what you cannot suture, but the stapling gun may facilitate and expedite the process. Some tissues are unsuitable for stapling, especially those that are very thin or very thick. Manual suturing allows a range of flexibility that is impossible to achieve with mechanical stapling instruments. Randomized controlled trials are few and new randomized studies are now unlikely to be initiated as stapling guns have become part of the regular armamentarium of the majority of colorectal surgeons. Nevertheless, some of the recent randomized trials have reported quite dramatic results, particularly in the leakage rate from ileocolonic anastomosis after right hemicolectomy[31] and recurrence rates following colonic cancer surgery[51]. While more carefully designed studies are needed to elucidate these issues further, the circular stapling gun, in particular, appears to have established its place as an indispensable asset in the hands of most colorectal surgeons.

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British Journal of Surgery 1996, 83, 910–912

Annales de Chirurgie

Digest

For this quarter's digest, Drs Pascal Frileux and Denis Castaing from *Annales de Chirurgie*, choose the best from issues one and two of 1996. A reciprocal digest written by our European Editor, Mr Colin Johnson, appears in the French journal.

Medullary carcinoma of the thyroid

The overall 5-year survival rate of patients operated on for medullary carcinoma of the thyroid is good. It has been estimated at 87 per cent in a recent report from a large German registry. Some prognostic factors have been established, but few multivariate analyses have weighed up the various clinical and biological criteria. Goudet *et al.*[1] have reviewed retrospectively a series of 51 cases, and have submitted the clinical, biochemical and immunocytological data to univariate and multivariate statistical analysis. Thirty-seven per cent of the patients had familial disease. Clinical variables tested were family history, age, sex, operation and stage of tumour (stage I: cancer localized to the thyroid; stage II: positive nodes; stage III: extension to neighbouring structures; stage IV: metastases). Biochemical variables were postoperative values of carcinoembryonic antigen (CEA) and calcitonin concentration in the serum. Immunocytochemical data were the intensity and percentage of uptake of CEA and calcitonin by the tumoral cells. The overall survival rate was 70 per cent at 5 years and 55 per cent at 10 years. Patients under 45 years of age, with familial disease, stage I/II tumour, and a normal CEA concentration in the serum had a significantly better prognosis. Also favourable were a weak intensity of CEA and calcitonin, and a high percentage of calcitonin uptake. The multivariate analysis identified age and early stage (I/II) as independent variables. The better prognosis of familial carcinoma compared with sporadic cases was mainly related to earlier diagnosis. Further studies are required to appreciate more precisely the prognostic impact of immunocytochemical data.

Colonic irrigation

Once a subject of a strong argument between American and British surgeons, colonic irrigation is now accepted as the best management of an end colostomy. Baumel *et al.*[2] from Montpellier carried out a national survey within the 'Fédération des stomisés de France', between March and July 1992. A questionnaire was sent to 3033 patients and 795 valid replies were collected (26 per cent). Fifty per cent of the patients were using irrigation. Those operated after 1980 and living in a urban area used irrigation more often than other patients. A local complication of the colostomy (prolapse, stenosis, hernia) reduced but did not prevent the use of irrigation. Among patients not using irrigation, 54 per cent regarded it as 'without benefit', 20 per cent as 'irrelevant' because of age, local complication or colitis, 18 per cent had tired of using it and 8 per cent were not aware of the procedure. Among patients using irrigation, 40 per cent had started shortly after operation and 80 per cent within 1 year. The mean volume was 1 litre and the mean frequency once every other day; a special diet was not necessary. Continence was good on the day of irrigation in all patients and minor leakage occurred in 50 per cent of patients the day after; 85 per cent were satisfied. Patients using irrigation wore a regular appliance (51 per cent), a small bag (33 per cent) or an obturating device (16 per cent). Ninety-six per cent of the patients using irrigation reported that they would continue to do so. Colonic irrigation is an efficient procedure, with very few patients choosing to stop the procedure. Its use is more frequent among members of an association than in non-affiliated persons (50 *versus* 25 per cent), and it is more often used as time goes by. The equipment now available is well adapted and safe, making the procedure simple to perform and easy to learn. The definitive frequency of irrigation (once every other day) can be implemented from the start and remains stable afterwards. Although most patients still wear a bag with irrigation, it is a precaution rather than a need.

Oesophageal replacement

Thomas *et al.*[3] from Marseille have accumulated a large experience of colonic interposition in the treatment of benign and malignant disease of the oesophagus. They report their experience in the years 1985–1995. Sixty patients underwent colonic interposition in this period, a sharp decrease compared with the previous decade (328 cases); this resulted from the development of gastroplasty (265 in the period 1985–1995). The indication for oesophageal replacement was cancer in 37 patients, benign stenosis in 13 and other diseases in ten. Choice of the colon was dictated by a previous or simultaneous gastrectomy ($n = 27$), a pharyngeal anastomosis ($n = 17$), a difficult dissection of the cardia because of previous surgery ($n = 6$) or was a deliberate choice in benign disease ($n = 10$).

In 53 patients the left colon was used, based on the left colic artery and inferior mesenteric vein in an isoperistaltic position. In the seven remaining cases, the arterial disposition was not favourable and the right colon was preferred. The interposed colon was placed in the oesophageal bed when possible (that is when a simultaneous oesophagectomy was performed; $n = 38$) and otherwise in the retrosternal space. The proximal anastomosis was done in the neck and the distal anastomosis was made either to the posterior aspect of the gastric antrum or to a jejunal Roux loop. Five patients (8 per cent) died and 39 patients (65 per cent) experienced postoperative complications. Three transplants became necrotic and had to be removed. At a median follow-up of 20 months, 25 patients were still alive while 30 had died from cancer recurrence ($n = 26$), brain damage ($n = 1$), iatrogenic perforation of the transplant ($n = 1$), suicide ($n = 1$) or pneumonia ($n = 1$). The functional results were considered good in 65 per cent of patients, fair in 25 per cent and poor in 10 per cent. Stenosis, regurgitation, fullness, diarrhoea, reflux and choking were the main symptoms. Such complications were particularly frequent in patients with lesions of the pharynx and larynx due to radiation or caustic injury.

Univariate and multivariate analysis showed that the position of the transplant (in the posterior mediastinum rather than in the retrosternal space) was the major determinant of the quality of the functional result. The authors acknowledge that gastric interposition has progressively replaced colon interposition in oesophageal replacement, but prefer coloplasty in benign disease as it allows maintenance of a gastric reservoir and prevents gastro-oesophageal reflux. When colonic interposition is selected, few preoperative investigations are necessary: colonoscopy and, in patients with arterial disease, arteriography. The best function is obtained with the left colon, in an isoperistaltic position, in the oesophageal bed, with maximal care being taken to avoid kinking of the colon. However, it remains a major procedure associated with significant morbidity and mortality rates. Long-term problems are minor but common, especially in the presence of abnormal swallowing.

Hepatectomy after prolonged intra-arterial chemotherapy

Elias *et al.*[4], from the Cancer Institute Gustave-Roussy, report a series of 14 hepatic resections performed after long-term intrahepatic arterial chemotherapy (IHAC) in patients with initially irresectable tumours.

These 14 cases represented 6 per cent of 239 patients who underwent IHAC and 4 per cent of 335 patients who had a hepatectomy for cancer in the same period. There were 13 metastases (nine colorectal tumours, four apudomas) and one hepatoblastoma. The mean number of IHAC sessions was 18 (range 6–48); eight patients had also received systemic chemotherapy. Chemotherapy decreased the tumour volume in 12 patients and stabilized it in two. Preoperative evaluation of liver function was by serum bilirubin concentration and clearance of indocyanine green, as advised by Makuuchi in cirrhosis. The volume of liver removed ranged from 20 to 60 per cent of the total volume (median 40 per cent). In all cases the hepatic tissue was fragile and friable, leading to bleeding (mean blood loss 2080 ml) and requiring a lengthy procedure (mean 5 h). There was no postoperative death. Eight patients had major complications: intraperitoneal bleeding ($n = 2$), perforated ulcer ($n = 1$), bile leak ($n = 2$), pneumonia ($n = 2$), and amaurosis ($n = 1$). In the long term three of the four patients with apudoma had a recurrence 12–75 months after resection and were treated either by chemotherapy or reresection; of the nine patients with colorectal cancer, four died at a median of 24 months after resection and five were alive without recurrence at a median of 9 (range 4–50) months after resection.

Resection after IHAC is rarely considered as this type of chemotherapy is usually prescribed for large and bilateral tumours; additionally, IHAC impairs liver function and this may preclude major hepatectomy. This is reflected by the low percentage (6 per cent) of patients who had resection after IHAC. In the literature, only 11 such cases have been reported, concerning hepatoblastoma in children and metastases from apudoma and colorectal cancer. The benefit of this procedure is difficult to appreciate in apudoma as few data are available for comparison. In metastatic colorectal cancer, the median survival with IHAC alone is 15 months, so these resections appear to be beneficial.

Resection after IHAC has some specific points, as this treatment modifies both the texture and functional value of the liver. Imaging is modified by the change in hepatic texture, and the best examination appears to be computed tomography with portal vein injection (T portography). The evaluation of liver function requires the same precautions as in hepatic cirrhosis, and the maximal resectable volume is best deduced from Makuuchi's formula based on indocyanine green clearance. The hepatic pedicle is modified by the previous surgical approach for catheter positioning and by the chemotherapy itself, the most common abnormality being arterial thrombosis. This obliges the surgeon to make a minimal dissection (if possible none) of the hepatic pedicle, in order to respect the collateral circulation. The liver resection should be done entirely by a parenchymal approach.

The liver parenchyma is soft, fragile and friable, and thus needs to be sectioned slowly, with careful clipping of tiny vessels. Bleeding from small hepatic veins is profuse because of increased venous pressure and venous dilatation. This may require the use of total vascular exclusion of the liver, either intermittent or in one stage. These difficulties are explained by the pathological modifications of the liver after IHAC: steatosis, sclerosing cholangitis, dilatation of the small hepatic veins and moderate cellular necrosis. Several instances of hepatic vein thrombosis have been encountered, suggesting a similarity between these lesions and veno-occlusive disease of the liver. In conclusion, hepatectomy after IHAC is more difficult, more lengthy, more bloody and more often complicated than surgery on normal parenchyma. It is rarely indicated but may, in specific cases, provide long-term survival and a hope of cure.

Long-term results of vertical banded gastroplasty for morbid obesity

Two techniques are now advised in the treatment of morbid obesity: vertical banded gastroplasty and horizontal gastroplasty plus Roux-en-Y anastomosis. Both procedures create a small gastric pouch with a slow emptying, thus producing an early sensation of fullness and a change in eating behaviour. The latter procedure creates a dumping syndrome that adds its own effect to the sensation of fullness and also reduces the rate of reflux, but is more complicated to perform. Gastroplasty for obesity produces a biphasic response: weight loss for 1 or 2 years and then stabilization. Frering *et al.*[5] have reviewed the long-term results of vertical banded gastroplasty in 62 patients, 55 women and seven men aged 20–68 (mean 37) years, operated on between 1987 and 1993. Preoperative mean weight and body mass index were 123 kg and 47 respectively. Associated diseases were diabetes ($n = 31$), hypertension ($n = 29$) and hyperlipaemia ($n = 21$). In all patients operation followed unsuccessful dietary regimens. The procedure used was application of a linear stapler from the cardia downwards, parallel to the lesser curvature, and placement of an annular band at the lower end of the staple line. At a mean follow-up of 3 years, the mean weight was 86 kg and the body mass index was 32. Three patients underwent removal of the band, either for vitamin B_1 deficiency ($n = 1$) or at their request ($n = 2$). Seven patients put on weight after an initial period of weight loss, in relation to staple line disruption in five patients or absorption of soft drinks (maple syrup syndrome) in two. Incisional hernia occurred in four patients and severe gastro-oesophageal reflux in ten, requiring permanent medication in eight and reoperation in two. Diabetes was corrected in 19 of 31 patients, hypertension in 19 of 29, and hyperlipaemia in 11 of 21. In 85 per cent of patients, both in the literature and in this series, significant weight loss can be obtained with suppression of metabolic complications in the majority of patients. However, major complications are frequent and the benefit to survival remains to be demonstrated.

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British Journal of Surgery 1996, 83, 912–914

Der Chirurg
Zeitschrift für alle Gebiete der operativen Medizin
Organ des Berufsverbandes der Deutschen Chirurgen e.V.
Organ der Deutschen Gesellschaft für Chirurgie

Digest

For this quarter's digest Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the December 1995 to March 1996 issues of *Der Chirurg*. A digest of the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Endocrine surgery

Medullary carcinoma of the thyroid or C cell carcinoma may develop sporadically or in patients with multiple endocrine neoplasia (MEN IIa/b) syndrome, the latter group accounting for approximately half the patients with C cell carcinoma. Inherited by an autosomal dominant trait, C cell carcinoma is preceded by C cell hyperplasia. Early identification and treatment of individuals at risk will improve prognosis. Such early detection has been based on a unique feature of the disease in that calcitonin provides a highly specific and sensitive tumour marker.

The development of C cell carcinoma is also strongly associated with a genetic defect causing mutation of the *RET* proto-oncogene, which may allow for even earlier diagnosis. Röher *et al.*[1] report experience with prophylactic thyroidectomy in asymptomatic patients from families with MEN with demonstration of *RET* proto-oncogene mutations. Between 1986 and 1995 a total of 121 patients were operated for C cell carcinoma. Of these 121 patients 51 were from known families with MEN, 19 had additional phaeochromocytoma and five patients had hyperparathyroidism.

Fifteen of 51 patients who underwent operation were symptomatic and 27 had pathological serum levels of calcitonin, but in nine patients aged between 3·5 and 30·0 years thyroidectomy was indicated because *RET* proto-oncogene point mutations had been demonstrated. All nine patients were asymptomatic, had normal ultrasonographic examinations and normal basal serum calcitonin levels. Stimulated calcitonin levels were normal in four of the nine patients, borderline in three and pathological in two. All nine patients underwent total thyroidectomy, with additional neck dissection in two.

C cell hyperplasia was defined as more than seven C cells per follicle, C cell clusters or more than 200 C cells per high-power (×200) field. C cell carcinoma was defined as C cell nests with infiltration of the basal membrane or destruction of the follicle. By these criteria, six patients were diagnosed as having multifocal C cell carcinoma (one with lymph node metastasis), two patients aged between 3·5 and 9·0 years had microcarcinoma and one had nodular hyperplasia. The authors recommend genetic screening at an early age and operative treatment before increased serum levels of calcitonin are demonstrable to ensure treatment of C cell carcinoma at an early stage.

Most surgeons will not require preoperative localization studies for patients with hyperparathyroidism, but in patients with previous operations to the neck, e.g. for thyroid disease or in patients with recurrent hyperparathyroidism, searching for parathyroid glands may occasionally be just a little trying. In such situations precise preoperative localization would be reassuring. Schoenemann *et al.*[2] from Stuttgart evaluated the use of ^{99m}Tc-methoxyisobutylisonitrile scintigraphy (^{99m}Tc-MIBI-scan) combined with single photon emission computed tomography (SPECT) for preoperative localization of enlarged parathyroid glands in a prospective study of 36 patients treated during a 12-month period in 1994. Seven of 36 patients had undergone previous operations for thyroid disease (five) or hyperparathyroidism (two). Of 37 enlarged glands, 27 with a mean weight of 2100 mg were demonstrated correctly by ^{99m}Tc-MIBI-scan and preoperative localization was correct in all seven patients who had previous surgery to the neck. The authors conclude that ^{99m}Tc-MIBI-scan is superior to thallium-technetium subtraction scintigraphy and represents a worthwhile diagnostic test for patients undergoing reoperative surgery for hyperparathyroidism as it is relatively easy to use with little discomfort to the patient.

In a paper by Böttger *et al.*[3] the value of preoperative localization studies in patients with hyperinsulinism is reviewed. During a 10-year period 28 patients with organic hyperinsulinism underwent surgical treatment. In patients with solitary lesions preoperative sonography localized only tumours larger than 1 cm in diameter, with a sensitivity of 41 per cent. Sensitivity of contrast-enhanced computed tomography (CT) was 55 per cent, 60 per cent for percutaneous transhepatic portovenous catheterization and 86 per cent for angiography. In contrast all 22 solitary adenomas could be palpated at operation and intraoperative ultrasonography visualized 20 of 21 adenomas examined.

Reviewing 41 articles from the literature, the authors determined that preoperative abdominal ultrasonographic studies had a sensitivity of 28 per cent compared with 84 per cent sensitivity of endosonography. CT was reported to have 32 per cent sensitivity, magnetic resonance imaging 59 per cent and angiography 54 per cent. Sensitivity of percutaneous transhepatic portovenous catheterization was recorded at 83 per cent and the more recent octreotide scintigraphy imaging technique was reported to have 63 per cent sensitivity (three articles reporting 38 patients). Interestingly, nine papers reported 181 patients with solitary occult adenoma not demonstrable by extensive preoperative studies, but 146 of these 181 adenomas were palpable at operation and 25 of 31 were demonstrable by intraoperative sonography for a combined sensitivity of 97 per cent. The authors conclude that preoperative localization studies are warranted only in patients with MEN syndrome to detect multiple adenomas or in patients with recurrent hyperinsulinism. As 95 per cent of patients without MEN syndrome will have solitary adenomas intraoperative palpation and ultrasonography will suffice to detect such lesions in the vast majority of patients. Extensive preoperative localization studies would appear to be of limited value in this group of patients.

Duodenal stump closure

Easy application and reliability have allowed widespread use of metal staplers in visceral surgery. More recently, stapling devices with absorbable staples have been developed, but as yet experience with their use is limited. The group from Offenbach[4] has now reviewed its experience with absorbable staples (copolymer lactomer; Polysorb, TA 55, USSC, Norwalk, Connecticut, USA) for duodenal stump closure and compared this with a historical control group in which metal staples (titanium clips; TA 30/55, USSC) were used. Between January 1985 and December 1991, 253 duodenal stump closures were performed with metal staples and 96 stump closures were carried out with absorbable staples. Although not randomized, the groups were similar regarding age, sex, diagnosis (64 and 67 per cent, malignant diseases) and type of operation (63 and 60 per cent total gastrectomies). Eighteen and 24 per cent of operations were performed as emergency procedures. The endpoint of the study was duodenal stump leakage demonstrated either radiologically by extravasation of contrast medium or at laparotomy. Contrast studies were performed routinely in all 349 patients between days 5 and 7 after operation with water-soluble contrast media. The time after which duodenal leaks were diagnosed was similar in the two groups (11·5 and 11·4 days respectively). When metal clips were used the leak rate was 8 per cent for patients with benign disease (87) and 3 per cent in patients with malignancy (166) for an overall anastomotic insufficiency rate of 5 per cent. When absorbable clips were applied the corresponding leak rates were 17 per cent for patients with benign disease (35) and 12 per cent for patients with a diagnosis of malignant disease (61). The overall leak rate for absorbable staples was 14 per cent. The authors conclude that the use of absorbable staples for duodenal stump closure cannot be recommended at present.

Rectal cancer

Technical refinements and due recognition of long available data regarding necessary safety margins have attracted much attention to sphincter-preserving operations for cancer of the lower rectum during the past decade. The group from Tübingen[5] has been among the protagonists of local treatment for selected low rectal cancers. They now report their experience with transanal endoscopic microsurgery (TEM) between 1989 and 1994. Patients with direct transanal excision of rectal lesions were excluded from this analysis. During the observation period 236 patients were treated by TEM. Postoperative pathological evaluation revealed rectal carcinoma in 98 patients. In 89 patients a full-thickness excision of the rectal wall was performed. Average operating time was 96 min. Four patients had intraoperative perforation of the intraperitoneal bowel wall and three patients had severe anastomotic leakage requiring Hartmann's procedure (two) or defunctioning colostomy (one). Nine patients had postoperative bleeding necessitating oversewing in two. In summary eight of 98 patients required reoperation for complications. Local tumour infiltration was recorded as pT1 (56), pT2 (27) and pT3 (15). Only 33 of 98 carcinomas were diagnosed before operation and notably nine of 15 pT3 carcinomas were considered adenomas before operation. Conventional radical reoperation was performed in eight of 54 low-grade pT1 carcinomas, because this was the patient's wish (five) or because margins were infiltrated (three). In addition, 18 of 27 patients with pT2 cancers and eight of 15 with pT3 tumours required reoperation for a total of 34 of 98 patients having reoperation to achieve radical oncological treatment after TEM. Pathohistological evaluation of 34 specimens revealed primary tumour residues in five patients and lymph node metastases in seven. At a median follow-up of 17 months, two of 46 patients treated with TEM alone for low-grade pT1 carcinoma and one of five patients with TEM for low-grade pT3 carcinoma developed recurrence. Although a high reoperation rate of almost 35 per cent appears disturbing this figure serves to document the critical attitude of the authors.

Even if a rectal cancer is located in the lower rectum and not amenable to local resection because of local infiltration, preservation of the sphincter may be possible in selected patients. Schumpelick and Braun[6] from Aachen report experience with intersphincteric resection in 119 patients treated between 1979 and 1994. Mean age of the patients was 59·5 (range 22–86) years. Although a distal free margin of 3 cm was generally attempted the actual margin was 2 cm in 44 patients. Excluded from intersphincteric resection were patients with uT2 tumours less than 4 cm above the anal verge and uT3 tumours less than 5 cm from the anal verge. Preoperative demonstration by anal manometry of sufficient sphincter function was considered a prerequisite for sphincter-saving procedures. The authors provide a detailed description of their operative technique which adheres to the principles of no-touch isolation and emphasize the need for total mesorectal excision and preservation of pelvic nerves. The inferior mesenteric artery is tied flush with the aorta and ventrally located aortocaval lymph nodes are removed. The authors usually performed stapled anastomosis (97) and placed a defunctioning colostomy or ileostomy (54), although they note a tendency to abandon a protective stoma. Pathohistological staging determined the following tumour stages: Dukes A (44), Dukes B (30) and Dukes C (45). Postoperative mortality was 3 per cent and the anastomotic leak rate was 8 per cent. Urinary retention and sexual dysfunctioin were observed in 16 and 17 per cent of patients respectively. Median follow-up was 6 years and ten of 114 patients with potentially curative operations developed local recurrence (9 per cent), mostly within 2 years of operation. Univariate analysis identified T stage, N status and grading as parameters significantly associated with the risk of local recurrence. Age-corrected 5-year survival was calculated at 71 per cent for the whole group and 100 per cent for Dukes stage A, 89 per cent for Dukes B and 48 per cent for Dukes C. Functional results were evaluable after a median follow-up of 6·6 years in 62 patients. Only two patients were considered grade IV incontinent and 11 patients reported occasional soiling. The authors speculate that intersphincteric rectal resection allows for more complete excision of the mesorectum thus reducing the risk of local recurrence compared with low anterior resection.

Liver metastases

While liver resection for colorectal metastases is widely practised, the indications for liver resection of non-colorectal metastases are less well defined. The groups from Hannover[7] and Mainz[8] have, therefore, examined their experience. The first paper reports 35 liver resections performed during an 11-year period in 34 patients with isolated liver metastases from breast cancer. Curative resections were performed in 86 per cent of the patients of which 56 per cent had solitary metastases. One patient died after operation and 5-year survival of curatively resected patients was 22 per cent, which is similar to that of patients with colorectal liver metastases. If R_0 resection was feasible, the stage of the primary tumour, the number and size of metastases and the extent of the hepatic resection were unrelated to outcome. The second article reports 30 liver resections performed for metastatic disease from a variety of primary tumours. Perioperative mortality rate was also 3 per cent and again 83 per cent of patients had a potentially curative R_0 resection. Five-year survival for this group was calculated as 45 per cent. Although based only on small numbers both reports confirm that liver resection is worthwhile for selected patients and should be considered for isolated hepatic metastases from non-colorectal cancers, if R_0 resection seems possible and the operative risk is low.

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British Journal of Surgery 1996, 83, 915–918

Management and follow-up of 78 giant haemangiomas of the liver

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The natural history and appropriate treatment of giant liver haemangioma remain poorly defined. The diagnostic strategy and the results of a longitudinal study of 78 such lesions are described. Sixteen resected patients and 62 with asymptomatic giant haemangiomas were entered into a follow-up programme consisting of clinical assessment and abdominal ultrasonography every 6 months. Resection was considered only for symptomatic patients (14 cases) and rapidly growing lesions (two cases). The mean follow-up was 36 months for the resected patients and 55 months for the observed group. Surgery permanently relieved symptoms. No recurrence of haemangioma was observed. Some 32 of 36 unresected lesions followed up remained stable in size. Minor changes were observed in four of 36. None ruptured or became symptomatic. It is concluded that asymptomatic large haemangiomas can be managed safely by observation. However, the occasional occurrence of rapid growth might represent a further indication for resection and justifies strict imaging follow-up. The pattern of growth, rather than absolute size, of a lesion is suggested for selection of asymptomatic patients who might benefit from preventive surgical excision. When feasible, the authors prefer enucleation to remove giant haemangiomas.

The incidental finding of liver haemangioma has increased considerably as so many patients undergo imaging of the upper abdomen for a variety of indications. Consequently a parallel growth in surgical referral for this condition, whether symptomatic or not, has been reported worldwide[1–3]. While there is general agreement that symptomatic haemangiomas should be excised, the proper management of asymptomatic lesions remains controversial. Giant haemangiomas, defined as those larger than 4·0 cm in diameter[4], are thought to behave differently from smaller ones, with a tendency to enlarge and, occasionally, rupture[5]. Therefore, the management of an asymptomatic giant haemangioma should be based on the balance between the outcome that might be prevented by surgical resection and the estimated operative risk. Furthermore, the distinct possibility of recurrence after resection, which has occasionally been reported, may lead to reoperation in a small subset of patients[6]. The scarcity of long-term longitudinal studies in the medical literature designed to describe and quantify the behaviour of unresected giant haemangiomas, and the fate of resected patients, accounts for the current existence of conflicting management policies[7].

The purpose of this study was to define, through ultrasonographic and clinical follow-up, the natural course of giant liver haemangiomas in patients elected for observational management and the long-term outcome of those undergoing surgical excision.

Patients and methods

Between 1 January 1988 and 31 December 1993 24000 patients underwent abdominal ultrasonography at this institution. A diagnosis of liver haemangioma was made in 402 (1·7 per cent) of patients examined. In 284 cases the haemangioma was single (*Table 1*) and ranged in size between 0·5 and 21·5 cm. In 78 patients (38 women and 40 men, mean age 55 (range 27–89) years) the lesion was larger than 4·0 cm and classed as a giant haemangioma. Since the growth of a haemangioma causes only compression of the surrounding parenchyma, it is usually possible to identify the originating liver segment even for very large lesions, by tracing the displaced hepatic veins and segmentary portal pedicles. The hepatic segments of origin of the 78 giant haemangiomas are indicated in *Table 2*. No patient was pregnant; 11 reported previous or concomitant oestrogen use for a mean period of 33 (range 5–43) months. Indication for ultrasonography in these patients was a mass in the liver suspected on clinical grounds in 52 cases and the presence of unrelated intra-abdominal disease in 26. The dimensions of all lesions were determined by ultrasonographic measurement in the transverse and sagittal planes. The presence of a grossly round lesion with irregular borders and a mixed appearance (hyperechoic and hypoechoic areas) was designated as typical of a giant haemangioma. However, this ultrasonographic pattern is nonspecific and varies considerably. A low-frequency or no signal on colour Doppler analysis was extremely helpful in confirming the diagnosis of haemangioma. When an atypical sonographic pattern was encountered, the diagnosis was established by angio computed tomography (CT) in 15 per cent of cases, magnetic resonance imaging (MRI) in 4 per cent and laparoscopy in one patient with concomitant ovarian cancer. Selective hepatic angiography in five symptomatic patients (6 per cent) with very large haemangiomas was only indicated to define the extrahepatic arterial anatomy and to provide a roadmap for surgical dissection. Five patients had ultrasonographically-guided fine-needle aspiration biopsy without complications.

Surgical excision of giant liver haemangioma was considered for symptomatic lesions (14 patients with either abdominal pain or epigastric discomfort) and rapidly growing haemangiomas (two patients) arbitrarily defined as those showing an increase in their largest diameter equal to or greater than 25 per cent within a 6-month period.

Sixty-two asymptomatic patients and 16 who underwent surgical resection were followed up as outpatients. Clinical

Table 1 Numbers of liver haemangiomas in 402 patients

No. of haemangiomas	No. of patients
1	284 (71)
2	60 (15)
3	16 (4)
4	11 (3)
>4	11 (3)
Bilateral haemangiomatosis	17 (4)
Right lobe haemangiomatosis	3 (1)

Values in parentheses are percentages

Paper accepted 10 February 1996

assessment and ultrasonography were performed every 6 months. For patients undergoing resection, operative mortality rate, occurrence of major complications and recurrence rate were evaluated. A Toshiba SA-250 (Tokyo, Japan) ultrasonographic scanner with a high-density crystal, high-definition 3·7 MHz transducer was used in all cases. Colour Doppler analysis was performed routinely during the last 3 years of the study using a Toshiba HG-140 scanner.

Results

Operative procedures

Sixteen patients with a diagnosis of giant liver haemangioma underwent operation. There were 14 women and two men with a mean age of 51 (range 31–69) years. The size of the haemangioma ranged from 4·5 to 15·0 cm. The rapid pattern of growth, which was the reason for operation in two patients, was observed at an early stage of follow-up ultrasonography, 6 months and 1 year after the initial diagnosis. The diameter of these two lesions at the time of resection was 7·0 and 8·5 cm. No specific feature at the time of initial presentation, such as age, previous hormonal treatment or associated pathology, could be identified retrospectively in these two patients to allow differentiation from those with stable haemangiomas. In both cases the sonographic appearance of the haemangioma was typical.

Simple enucleation was performed in 11 patients; in three this was combined with cholecystectomy and in one with right adrenalectomy for an incidental phaeochromocytoma. Formal right hepatectomy was the operative procedure in three patients, and left lateral segmentectomy and right lateral segmentectomy in one patient each. The mean operative blood loss in the whole series was 400 (range 150–1500) ml; in the last eight patients in whom the haemangioma was enucleated with temporary inflow occlusion (Pringle manoeuvre) the mean blood loss was 150 (range 100–200) ml. There were no operative deaths. One patient developed an external biliary fistula after a right hepatectomy which was managed conservatively and healed in 4 weeks.

Postoperative follow-up

No operated patient was lost to follow-up. During the period of follow-up, which ranged from 12 to 71 (mean 36) months, no recurrence of haemangioma was observed. All patients remained free from their previous symptoms.

Observational management

Because the main purpose of this study was to monitor possible changes in size of unresected cavernous haemangiomas, 20 non-surgical patients living in distant areas from the hospital who could not participate in the ultrasonography follow-up protocol were excluded from the subsequent analysis. However, they were interviewed by telephone and none reported the development of symptoms or presented elsewhere for treatment. Six further non-surgical patients died from unrelated diseases. In the follow-up period ranging between 16 and 72 (mean 55) months, 32 of the remaining 36 haemangiomas remained stable. In three a slight increase in size (0·5 cm) was observed, while one showed a decrease in diameter of 0·6 cm. These minor size changes always occurred in haemangiomas of 8·0 cm or less in diameter. No patient has become symptomatic.

Table 2 Hepatic segments from which 78 giant liver haemangiomas originated

Liver segment	No. of patients
I	1 (1)
II	4 (5)
III	6 (8)
IV	8 (10)
V	5 (6)
VI	20 (26)
VII	28 (36)
VIII	6 (8)

Values in parentheses are percentages

Discussion

Management of giant liver haemangiomas ranges from observation to surgical resection[7,8]. Non-surgical treatments have also been reported with restricted indications and limited success[9]. Deciding which patient should be operated on depends on the balance between the operative risk and the natural history of untreated lesions[10]. While the first is dependent on the surgeon's experience and, in uncomplicated cases, should be negligible[11], the second is still unclear because of the indeterminate behaviour of large non-resected lesions.

Abdominal pain or discomfort was the commonest indication for surgical excision in these patients. Surgical exploration has also been advocated to establish an uncertain diagnosis, particularly when malignancy cannot be ruled out[2,3]. This concept was supported by the observation that the imaging diagnosis of liver haemangioma was occasionally found to be incorrect at operation[2]. Various imaging techniques proved to be reliable in establishing a diagnosis of giant haemangioma. Although the ultrasonographic pattern of this disease can sometimes be similar to that of primary or metastatic liver tumours, a confident diagnosis was established by ultrasonography combined with colour Doppler analysis in 85 per cent of patients studied[12,13]. The use of technetium-99m labelled red blood cell scintigraphy to diagnose liver haemangiomas larger than 2 cm is well documented[14] and, in atypical situations, remains a reasonable choice. However, this technique does not offer the same degree of anatomical information (precise location of the lesion within the liver and relationship with surrounding intrahepatic vessels) as that provided by high-resolution abdominal imaging, notably contrast CT and MRI. This information can be important in planning the surgical procedure. When an atypical appearance is seen on sonography, resection may be required. The authors' choice of investigations would be contrast-enhanced CT, MRI and, only if necessary, scintigraphy. In the present study, 15 per cent of haemangiomas with an atypical sonographic appearance were clearly identified on

Table 3 Size range of operated and observed haemangiomas

	Diameter (cm)			
	4·0–5·9	6·0–7·9	8·0–9·9	≥ 10·0
Operated ($n = 16$)	2	5	2	7
Observed ($n = 62$)	35	18	7	2

contrast CT, while in 6 per cent of patients MRI was also required to establish the diagnosis. The combination of these techniques provided tissue-specific characterization of the haemangioma in all patients and obviated the need for further investigations to confirm the diagnosis.

Fine-needle biopsy was performed in five patients with known extrahepatic primary cancer at the time of initial ultrasonographic assessment. Although no bleeding occurred following this procedure the potential for this complication, and the ability to establish a confident diagnosis in most patients by non-invasive imaging techniques, led the authors to conclude that percutaneous biopsy of suspected haemangioma should only be considered when the results of non-invasive tests are inconclusive.

In atypical situations, laparoscopy can also be of value[3,15]: when haemangiomas are situated in the subcapsular tissue, they are readily recognized on gross examination and by gentle palpation which reveals compressibility, a finding which is practically restricted to vascular lesions. In addition, this technique can be effectively combined with laparoscopic contact ultrasonography which significantly adds to the diagnostic potential of laparoscopy alone[16]. Thus, the indication for diagnostic laparotomy in giant liver haemangiomas is relatively restricted.

Seven of nine patients in this series with a lesion exceeding 10 cm diameter presented with symptoms and were operated on compared with only two of 37 whose haemangioma ranged between 4·0 and 5·9 cm (*Table 3*). It is concluded that symptoms are more often associated with very large haemangiomas. It was also suggested that haemangiomas exceeding 10 cm in diameter may have a greater potential for internal bleeding, further growth or rupture[2]. This observation would justify prophylactic excision of asymptomatic large lesions. However, the initial diameter of the two rapidly growing haemangiomas in this series was in both cases smaller than 10 cm. Furthermore, minor changes in size were observed at follow-up ultrasonography only with lesions ranging between 4·0 and 7·9 cm diameter. It appears that size alone is a poor predictor of the subsequent behaviour of asymptomatic haemangiomas and should not be an absolute indication for surgery. The authors believe that the pattern of growth as assessed by repeat ultrasonography or CT could be used to decide which asymptomatic patient might benefit from preventive surgical excision. A minimum 25 per cent increase in the largest diameter within a period of 6 months was arbitrarily chosen in this study to characterize rapidly growing lesions. The observation that most malignant hepatic tumours exhibit a similar pattern of growth provides the rationale to support the choice of this threshold in selecting patients for surgical treatment. Although the natural history of these rapidly growing lesions remains unresolved by this study where they were resected, the potential for rupture or diagnostic error is expected to be higher in this group of patients, making resection a reasonable choice. The attempt to identify specific clinical features or imaging clues that might help to select the small percentage of patients whose liver haemangiomas will exhibit rapid growth was unsuccessful in these patients.

When surgical excision is indicated, enucleation combined with temporary inflow occlusion allows safe removal of giant haemangiomas with minimal blood loss and preservation of all normal liver tissue[17,18]. However, in the authors' view, very large lesions occupying most of a liver lobe or deeply located within the hepatic parenchyma can be very difficult to enucleate and are best managed by formal hepatectomy.

It is concluded that surgical treatment should mainly be considered for symptomatic patients, since in the other patients the occurrence of symptoms or spontaneous rupture should be regarded as exceptional. Rapidly growing haemangiomas might represent a further indication for resection, although the natural course of these lesions is unknown. The unpredictable, occasional exhibition of rapid growth, which is more likely to occur during the early phase of observation, justifies follow-up imaging of all asymptomatic haemangiomas at regular intervals. The need to continue the follow-up when no growth has been seen after a sufficiently long period of time remains to be defined. When removal of the lesion is indicated, enucleation is the authors' treatment of choice. Since the risk of overlooking malignant lesions should never be underestimated, laparoscopy in combination with laparoscopic contact ultrasonography is proposed as an effective tool to establish the presence of superficial haemangiomas in patients with uncertain diagnosis.

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British Journal of Surgery 1996, 83, 918

Case report

Simultaneous aortorenal homograft transplantation: expanding the indications for renal and vascular replacement

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Renal transplantation is the ideal solution for end-stage renal disease. Results are good with proper immunosuppression and immunological monitoring. Orthotopic and heterotopic transplantation work well as technical options. Renal disease is, however, associated with medial calcification of the arterial wall; this is usually diffuse, involving long arterial segments. Such calcification can technically preclude transplantation.

The use of homografts in cardiovascular surgery is not new; cardiac valve homografts have been used for some time[1,2]. Vascular replacement with arterial homografts was attempted in the 1940s and there is renewed current interest in cryopreservation[3].

Case report

A 44-year-old man with end-stage renal disease considered for transplantation was assessed by computed tomography and digital subtraction angiography. A tortuous splenic artery precluded orthotopic transplantation. A right iliac aneurysm and extensive diffuse aortoiliac calcification were also demonstrated. The patient was deemed technically unsuitable for heterotopic transplantation despite his 70-year-old mother being an ideal donor. Initially, he was expected to be restricted to haemodialysis.

As the authors had 5 years' experience with homotransplantation of valves and arteries, a decision was made to perform simultaneous aortoiliac homotransplantation. On 8 February 1995 a left donor nephrectomy was carried out. A transverse laparotomy confirmed extensive diffuse calcification of the recipient aortoiliac segment. A cryopreserved bifurcation homograft (12 × 6 mm) was sewn end to side to the subrenal aorta. The limbs of this homograft were anastomosed to the distal common iliac arteries in a less calcific sector. The renal vein was anastomosed to the inferior vena cava and the renal artery to the right leg of the homograft. Immediate urine production was noted. A Leadbetter–Politano ureter-to-bladder anastomosis was performed. Urine output rose to 5000 ml over the first day. The recipient was discharged 12 days after operation while receiving cyclosporin. Creatinine level was 114·92 μmol/l.

Discussion

A significant number of patients with renal disease present with severe arterial pathology[4]. In addition to the present case, the authors have performed vascular reconstruction with cryopreserved arterial homografts before renal transplantation in five further patients. Aortoiliac calcification and the calcified splenic artery in the patient described here precluded any attempt at transplantation by the standard techniques. The use of a cryopreserved bifurcation homograft was the only possibility of allowing implantation of a renal graft. To the authors' knowledge, this is the first successful combined procedure. This satisfactory outcome and the authors' other acceptable results with vascular homografts[5] might represent the start of an expansion in transplant possibilities for end-stage renal disease. Further experience is needed to confirm this initial impression.

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Paper accepted 5 September 1995

British Journal of Surgery 1996, 83, 919–923

Increased monocyte cytokine production in association with systemic complications in acute pancreatitis

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Tumour necrosis factor (TNF) α, interleukin (IL) 1β, IL-6 and IL-8 are thought to play a central role in the pathophysiology of sepsis but their role in acute pancreatitis is unknown. In the present study, monocytes were isolated from the peripheral blood of 26 patients with moderate or severe acute pancreatitis without biliary sepsis. Secretion of these cytokines *in vitro* was measured at intervals during the first week of illness. Sixteen patients developed systemic complications. Peak TNF-α secretion was significantly higher in patients who developed systemic complications (median (interquartile range (i.q.r.)) 18·5 (5·5–28·5) ng/ml) than in those with an uncomplicated course (3·7 (2·3–6·4) ng/ml, $P<0·01$). Similarly, peak IL-6 and peak IL-8 secretion were significantly higher in the complicated group (IL-6: complicated median (i.q.r.) 48·9 (12·1–71·0) ng/ml, uncomplicated 16·3 (14·2–37·9) ng/ml, $P<0·05$; IL-8: complicated 748 (643–901) ng/ml, uncomplicated 608 (496–749) ng/ml), $P<0·05$). No significant difference in peak IL-1β secretion was observed between the two groups. Systemic complications of acute pancreatitis are associated with a significant increase in monocyte secretion of TNF-α, IL-6 and IL-8 suggesting that, as in sepsis, these cytokines play a central role in the pathophysiology of the disease.

Severe acute pancreatitis is commonly associated with a systemic illness characterized by a hyperdynamic circulation[1,2] with varying degrees of impairment of respiratory and renal function. At the extreme end of the spectrum, patients develop multiple organ failure with an associated high mortality rate. This systemic illness has many similarities to that seen in patients with sepsis and it has been postulated that similar pathophysiological mechanisms may underlie the systemic manifestations of both conditions[3]. In sepsis, there is now considerable evidence that the systemic illness is the result of uncontrolled activation of mononuclear phagocytes and the consequent release of increased quantities of inflammatory mediators. Among these, tumour necrosis factor (TNF) α, interleukin (IL) 1β, IL-6 and IL-8 are thought to play an important role[4]. In contrast, the pathophysiology of the systemic illness seen in acute pancreatitis is unknown. For many years it was considered to be the result of activated proteases released from the damaged pancreas and the consequent local and systemic release of vasoactive peptides[5–7]. However, the failure of antiprotease therapy to influence the outcome of acute pancreatitis[8–12] has led to reappraisal of this theory and the search for alternative mechanisms.

Previous authors have demonstrated that plasma levels of IL-6 are increased in patients with complicated or fatal acute pancreatitis[13,14] and IL-6 levels have been reported to have prognostic significance early in the course of the disease[14]. Plasma levels of TNF-α have been measured in two studies with inconclusive results[15,16]. There have been no studies examining IL-1β or IL-8 secretion in acute pancreatitis. The interpretation of studies of plasma cytokine levels is made difficult by the presence of circulating inhibitors[17,18], the short half-life of many cytokines in the circulation[19] and the fact that their main physiological action is at a paracrine level[20]. TNF-α, IL-1β, IL-6 and IL-8 are mainly products of activated mononuclear phagocytes and so, to study further their role in acute pancreatitis and to avoid the potential pitfalls of plasma cytokine measurement, the secretion of these cytokines was examined *in vitro* by monocytes isolated from patients with acute pancreatitis during the first week of illness.

Patients and methods

Patients

Twenty-eight consecutive patients entered into a randomized controlled trial of the long-acting somatostatin analogue, octreotide (Sandostatin, Sandoz Pharma, Basle, Switzerland), were studied. Acute pancreatitis was defined as a rise in serum amylase to greater than four times the upper reference limit, associated with a typical clinical picture involving upper abdominal pain and vomiting. Patients were selected on the basis of an admission Acute Physiology and Chronic Health Evaluation (APACHE) II score of greater than five[21] in order to focus on the more severely ill patients. All patients were assessed daily for 5 days by one observer and thereafter at intervals until discharge. Inpatient morbidity and mortality was recorded.

Of the 28 patients studied, 14 were women. Their mean age was 58 (range 25–92) years. Gallstones were identified as a cause of acute pancreatitis in 16. Of the remainder, nine gave a history of chronic alcohol excess and in three patients the aetiology of acute pancreatitis was not identified. The delay from onset of symptoms to the first blood sample varied from 12 to 102 h (median of 36 h).

Systemic complications were defined as follows:

1. Pulmonary insufficiency: arterial partial pressure of oxygen below 60 mmHg.
2. Renal failure: serum creatinine concentration greater than 180 μmol/l despite fluid resuscitation.
3. Shock: systolic blood pressure less than 90 mmHg.

Two patients had evidence of cholangitis, as defined by the presence of jaundice, fever and leucocytosis and, in view of the known effect of sepsis on cytokine production, these patients were excluded from further analysis. Both had an otherwise uncomplicated clinical course.

Of the remaining patients, sixteen of 26 developed systemic complications, of whom five died. Twelve patients developed pulmonary insufficiency, two had acute renal failure and a

Presented to the Surgical Research Society in Glasgow, UK, July 1994

Paper accepted 20 September 1995

further two developed multiple organ failure. Of the five patients who died, two died in the first week with fulminant pancreatitis. One patient died in the second week with post-mortem evidence of a recent myocardial infarction and pancreatic necrosis. Two patients died in the third week, one following necrosectomy for infected pancreatic necrosis and one with bronchopneumonia.

Methods

Venous blood was withdrawn into sterile tubes containing 2·4 per cent ethylenediamine tetra-acetic acid on the first, third and fifth day after admission where possible. Blood was immediately transported to the laboratory at room temperature and peripheral blood mononuclear cells (PBMC) were separated by centrifugation on a Ficoll gradient (Lymphoprep; Nycomed, Birmingham, UK). Monocytes were separated from PBMC by an immunomagnetic technique (MACS; Becton Dickinson, Oxford, UK). Briefly, PBMC were incubated with anti-CD14 monoclonal antibody (Leu M3; Becton Dickinson) which was conjugated with metallic microbeads. These microbeads are small (50–100 nm) and do not interfere with cell viability or function[22]. The cell suspension was then passed through a matrix suspended within a powerful magnetic field where antibody-bound cells were retained and unbound cells were washed through. Retained cells were eluted from the matrix outside the magnetic field. These cells were collected by centrifugation and resuspended in serum-free medium (AIM-V, Gibco, Paisley, UK). Using this method, monocyte purity was 92 ± 5 per cent as assessed by flow cytometry. A viable cell count was performed by trypan blue exclusion and cells were then adjusted to a density of 5×10^5 viable cells per ml. Viability was always greater than 95 per cent. Cells were stimulated with bacterial lipopolysaccharide (LPS; *Escherichia coli* 055 B5, 200 ng/ml; Sigma, Dorset, UK) and cultured for 24 h at 37°C in a 5 per cent carbon dioxide humidified atmosphere. After 24 h in culture, the supernatant was removed, clarified by centrifugation and frozen at − 30°C.

Cytokine assays. TNF-α was measured using an in-house enzyme-linked immunosorbent assay (ELISA). This was based on a double antibody sandwich technique using polyclonal anti-TNF-α as coating antibody (Genzyme, Cambridge, Massachusetts, USA) and monoclonal anti-TNF-α (Boehringer-Mannheim, East Sussex, UK) as secondary antibody. Bound secondary antibody was then quantified using biotinylated antimouse monoclonal antibody followed by streptavidin-conjugated alkaline phosphatase (both Boehringer-Mannheim). Plates were read at 415 nm and results were calculated against a standard curve which was generated with serial dilutions of recombinant TNF-α (Genzyme). The sensitivity of the assay was 0·15 ng/ml. The interplate variability was 12·5 per cent and the intraplate variability was 13 per cent.

IL-6, IL-1β and IL-8 were measured using commercially available ELISA kits (Amersham International, Amersham, UK).

Statistical analysis was by the Mann–Whitney *U* test.

Results

Tumour necrosis factor α

Peak LPS-stimulated TNF-α secretion was higher in cells purified from patients with systemic complications (median (interquartile range (i.q.r.)) 18·5 (5·5–28·5) ng/ml than in those obtained from patients with an uncomplicated course (3·7 (2·3–6·4) ng/ml, $P<0{\cdot}01$). The highest levels of TNF-α secretion were seen on days 1 and 3 after admission and were significantly higher in the complicated group (*Fig. 1*). There was a significant positive correlation between peak TNF-α secretion and the severity of the systemic illness as assessed by the maximum Acute Physiology Score (APS, a component of the APACHE II score[23]) during the 5 days of study ($r=0{\cdot}678$, $P<0{\cdot}001$).

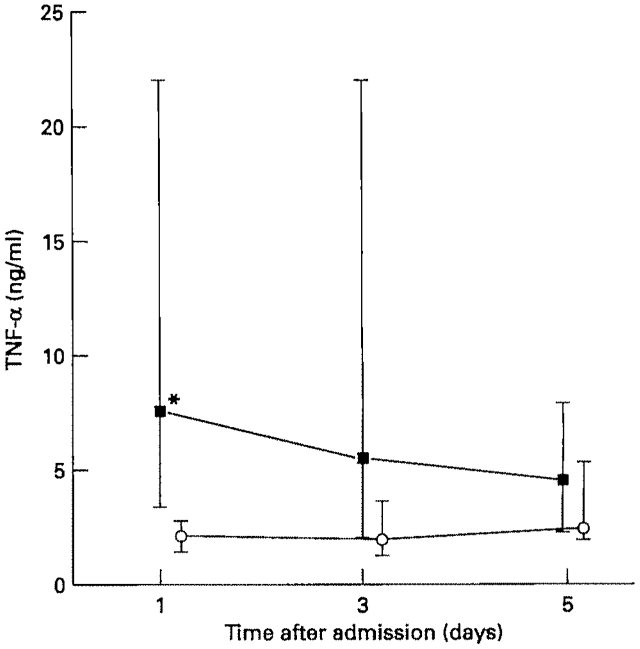

Fig. 1 Monocyte tumour necrosis factor (TNF) α secretion in acute pancreatitis. ■, Patients with systemic complications; ○, patients with an uncomplicated course. Values are median (interquartile range). $^*P<0{\cdot}01$ *versus* uncomplicated course (Mann–Whitney *U* test)

Interleukin 6

Peak IL-6 secretion was significantly higher in cells from patients who developed systemic complications (median (i.q.r.) 48·9 (12·1–71·0) ng/ml) than in those from patients with an uncomplicated course (16·3 (14·2–37·9) ng/ml, $P<0{\cdot}05$). Highest levels of IL-6 secretion were also seen on days 1 and 3 after admission and on these days the levels were significantly higher in the complicated group (*Fig. 2*). There was a significant correlation between peak IL-6 secretion and the peak APS ($r=0{\cdot}515$, $P<0{\cdot}01$) and between peak IL-6 and TNF-α secretion ($r=0{\cdot}672$, $P<0{\cdot}001$).

Interleukin 8

Peak IL-8 secretion was significantly higher in cells from patients with systemic complications (median (i.q.r.) 748 (643–901) ng/ml), than in those obtained from patients with an uncomplicated course (608 (496–749) ng/ml, $P<0{\cdot}05$). The highest levels of IL-8 secretion were observed on days 1 and 3 (*Fig. 3*) and there was a positive correlation between peak IL-8 secretion and peak APS ($r=0{\cdot}405$, $P<0{\cdot}05$).

Interleukin 1β

In contrast to the findings with TNF-α and IL-6, systemic complications were not associated with significantly higher peak IL-1β monocyte secretion (complicated group median (i.q.r.) 2·9 (1·4–3·4) ng/ml, uncomplicated group 1·6 (1·2–1·9) ng/ml, *P* not significant) although significantly higher levels of IL-1β secretion were observed on day 5 in cells from the complicated group (*Fig. 4*). There was no significant correlation between peak IL-1β secretion and peak APS or between peak IL-1β secretion and peak TNF-α or IL-6 secretion.

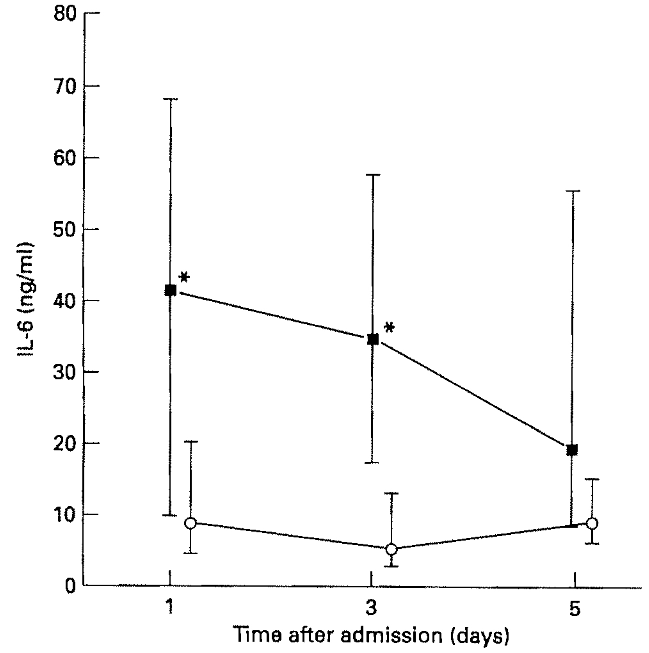

Fig. 2 Monocyte interleukin (IL) 6 secretion in acute pancreatitis. ■, Patients with systemic complications; ○ patients with an uncomplicated course. Values are median (interquartile range). $^{*}P < 0.02$ *versus* uncomplicated course (Mann–Whitney *U* test)

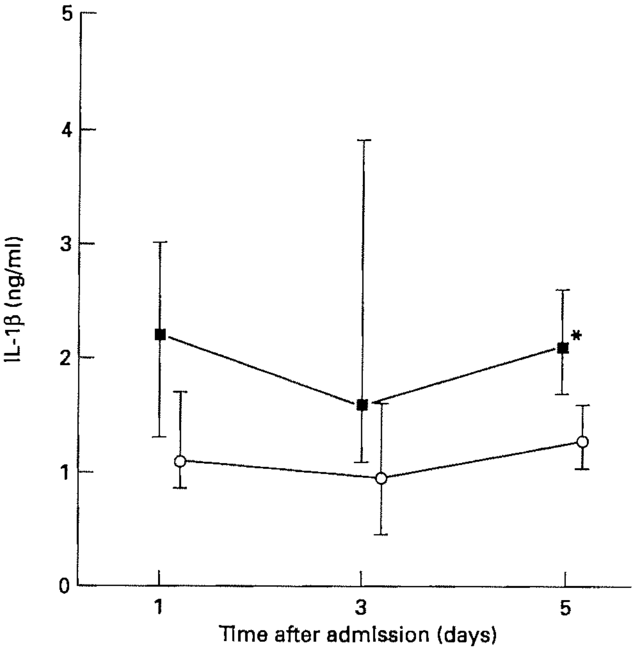

Fig. 4 Monocyte interleukin (IL) 1*β* secretion in acute pancreatitis. ■, Patients with systemic complications; ○, patients with an uncomplicated course. Values are median (interquartile range). $^{*}P < 0.05$ *versus* uncomplicated course (Mann–Whitney *U* test)

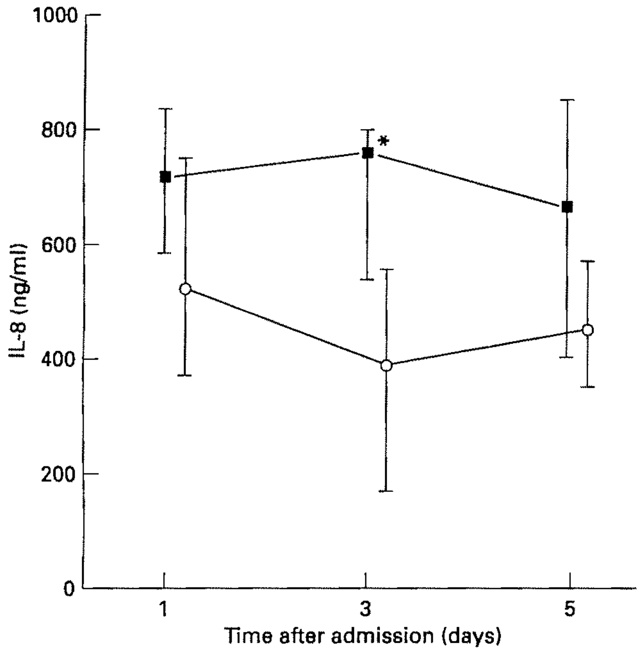

Fig. 3 Monocyte interleukin (IL) 8 secretion in acute pancreatitis. ■, Patients with systemic complications; ○, patients with an uncomplicated course. Values are median (interquartile range). $^{*}P < 0.02$ *versus* uncomplicated course (Mann–Whitney *U* test)

Influence of aetiology and therapy

Of the 16 patients who developed systemic complications, eight had evidence of gallstones. There was no significant difference in peak secretion of any cytokine between cells from patients with gallstone-related acute pancreatitis and from those with acute pancreatitis of other aetiologies.

The possible effect of octreotide on cytokine secretion was examined. Ten of 14 patients in the octreotide group developed complications compared with six of 12 in the placebo group. There were no significant differences in peak TNF-α, IL-1*β*, IL-8 or IL-6 secretion between patients receiving octreotide and those receiving placebo.

Discussion

This study has demonstrated for the first time that monocyte secretion of the proinflammatory cytokines, TNF-α, IL-6 and IL-8, is increased in patients with systemic complications in acute pancreatitis. There was also a strong correlation between peak IL-6, IL-8 and TNF-α secretion and the peak APS. These findings, coupled with the known physiological effects of TNF-α, IL-8 and IL-6, strongly suggest that these cytokines are early mediators of the systemic illness in acute pancreatitis. Peak values were studied to avoid difficulties in comparison of samples from patients at different times from the onset of symptoms.

It is well recognized from previous reports that raised plasma levels of IL-6 are present in patients with severe acute pancreatitis, with peak levels occurring within the first 3 days after admission[13,14]. In the present study, peak monocyte IL-6 secretion was observed within the first 3 days following admission, which is similar to the time course of the peak in plasma levels observed by previous authors. This provides further evidence that IL-6 is involved in the mediation of the systemic illness associated with acute pancreatitis and suggests that mononuclear phagocytes are the principal source of IL-6 in acute pancreatitis.

Previous studies of TNF-α in the peripheral blood of patients with acute pancreatitis have given inconclusive results[15,16]. However, by measuring plasma levels of TNF-α, these studies take no account of possible transient rises in TNF-α nor of increased TNF-α production at a cellular level. The presence of TNF-α inhibitors and binding proteins further complicates the measurement of plasma TNF-α and makes the interpretation of negative results difficult[17]. By studying monocyte TNF-α secretion directly, the present study avoids these difficulties and provides a measure of the activation status of mononuclear phagocytes at each time point which it is assumed reflects the likely behaviour of these cells *in vivo*. The present study provides the first conclusive evidence of a role for TNF-α in the mediation of the systemic complications of acute pancreatitis.

No evidence was found of a rise in monocyte IL-1β secretion in association with systemic complications. It is interesting to note that reports of serum levels of IL-1β in human sepsis give variable results and, unlike TNF-α and IL-6, levels of IL-1β do not appear to correlate with mortality rates[24,25]. There are no published reports of plasma IL-1β levels in acute pancreatitis and the role, if any, of this cytokine in acute pancreatitis remains unclear.

IL-8 is a potent activator of neutrophils and may be involved in the development of lung injury[26]. In the present study, IL-8 secretion by monocytes was increased in association with the development of systemic complications and reports are now beginning to appear suggesting that serum IL-8 levels are increased in patients with acute pancreatitis[27,28].

Four patients who developed severe systemic complications had levels of monocyte cytokine secretion similar to those in patients in the uncomplicated group. One explanation for this may have been a delay in presentation, allowing the peak in cytokine secretion to be missed. However, the time from onset of symptoms to the first blood sample in this group was similar to that in the remainder of the patients. Three of these patients had alcohol-related acute pancreatitis and this raises the possibility that cytokine secretion may be partly dependent on aetiology. Alcohol has a variety of effects on the immune system and has been shown to down-regulate TNF-α production by human monocytes[29]. However, raised levels of cytokine secretion were found in other patients with alcoholic pancreatitis and overall there was no difference in peak cytokine secretion in patients with pancreatitis due to gallstones and those with pancreatitis of other aetiologies.

Octreotide has been reported to stimulate reticuloendothelial function *in vivo*[30] and monocyte function *in vitro*[31] and the possible influence of its administration to some patients in this study was considered. However, peak levels of cytokine secretion were similar in patients receiving octreotide and those receiving placebo and a similar systemic complication rate was observed in the two groups of patients. There was therefore no evidence that octreotide administration influenced the results obtained. However, the number of patients studied was insufficient to exclude such an effect.

The main stimulus to mononuclear phagocyte activation is bacterial endotoxin. For many years it has been known that patients with severe acute pancreatitis frequently have endotoxaemia[16,32,33] and that this is more commonly observed in patients with complicated disease. In acute pancreatitis, the combination of a reduction in splanchnic blood flow and local peritonitis may result in an increase in transluminal absorption of endotoxin with subsequent passage through the portal circulation. Impaired hepatic reticuloendothelial function, which has been reported in some patients with severe acute pancreatitis[34], may facilitate the passage of endotoxin into the systemic circulation. This sequence of events may explain the activation of circulating mononuclear phagocytes observed in this study.

In summary, increased monocyte release of the inflammatory cytokines TNF-α, IL-8 and IL-6, but not of IL-1β, has been demonstrated in association with the development of systemic complications of acute pancreatitis. This provides evidence that the systemic effects of acute pancreatitis may be mediated by activation of mononuclear phagocytes and increased cytokine release which, if confirmed by further study, may lead to trials of new therapeutic agents designed to modulate this aberrant host response.

Acknowledgements

The authors acknowledge the assistance of the consultant surgeons and their junior staff at Glasgow Royal Infirmary, Stobhill General Hospital, Southern General Hospital, Victoria Infirmary, Monklands General Hospital, Law Hospital, Hairmyres Hospital and Vale of Leven Hospital for allowing the inclusion of their patients in this study. This study was supported by Greater Glasgow Health Board Research Support Group and Sandoz Pharma.

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British Journal of Surgery 1996, 83, 924–929

Early localization of necrosis by contrast-enhanced computed tomography can predict outcome in severe acute pancreatitis

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A total of 161 primary contrast-enhanced computed tomography (CT) scans of patients with acute necrotizing pancreatitis taken between 1982 and 1994 were analysed retrospectively. The aim was to assess the prognostic significance of the extent and anatomical site of pancreatic tissue necrosis in the first contrast-enhanced CT scan. The scans were obtained a mean of 2·9 days after the onset of symptoms. The pancreatic head was affected in 107 patients, the body in 119 and the tail in 138. Pancreatic tissue necrosis, when divided into four groups according to anatomical site, correlated with overall clinical outcome. The anatomical site of necrosis was clearly better than its crude extent in predicting the risk of complications. For patients with necrosis in the head of the pancreas, the outcome was as severe as when the entire pancreas was affected. In contrast, for patients with necrosis only in the distal part of the pancreas, the outcome was favourable with few complications. The exact site of pancreatic tissue necrosis should be known when early contrast-enhanced CT is used in prognostic scoring.

The spectrum of acute pancreatitis ranges from a mild spontaneously resolving disorder to severe disease with a mortality rate of up to 45 per cent[1]. Early diagnosis and assessment of severity in acute pancreatitis are still far from ideal. Clinical evaluation on admission is not accurate[2,3]. C-reactive protein (CRP) level is the most promising laboratory marker of severity, even though it is not specific for pancreatitis[4]. Multiple-factor prognostic scoring systems, such as Ranson's early prognostic signs[5], modifications of this by Imrie[6] and McMahon *et al.*[3], and Acute Physiology And Chronic Health Evaluation[7] (APACHE) II score have been shown to have predictive value, but their complexity limits routine use in daily clinical practice.

Contrast-enhanced computed tomography (CT) is the imaging technique of choice for the non-invasive assessment of severity in acute pancreatitis[8,9]. Low enhancement values of pancreatic tissue below 30 Hounsfield units (HU) with 400 mg iodine per kg body-weight and peripancreatic inflammatory changes in early-phase CT are clearly correlated with the clinical severity of disease, the development of complications and the mortality rate[10]. Two different CT-based indices of severity have recently been introduced, one based on the amount of pancreatic tissue necrosis and peripancreatic inflammation[11] and the other purely on the extent of pancreatic necrosis[12]. In these severity indices the site of necrosis is not considered, only its total extent.

The aim of the present study was to determine the prognostic significance of the extent and site of pancreatic tissue necrosis in severe acute pancreatitis, as analysed by contrast-enhanced CT.

Patients and methods

Patients

Between January 1982 and October 1994 there were 2797 admissions for acute pancreatitis to the Second Department of Surgery at Helsinki University Central Hospital. CT was performed on 380 patients in the acute phase of the disease because severe pancreatitis was suspected on clinical grounds. The following clinical features were used: abdominal pain, vomiting, fever, tachycardia, increased tenderness, rebound, distension, bowel paralysis, Grey Turner's sign or Cullen's sign with raised amylase levels. Amylase thresholds were over 500 mmol/l (normal range <300 mmol/l) in serum and over 5000 mmol/l (normal range <2000 mmol) in urine. In 210 of these scans the diagnosis of severe acute necrotizing pancreatitis was verified by clinical, laboratory, radiological, operative and autopsy findings. On account of defective renal function preventing the use of contrast medium, the fulminant course of the disease or a change in CT strategy during the early phase, data on early contrast-enhanced CT were available for analysis in only 161 patients.

These were 144 men and 17 women of mean age 40 (range 19–74) years. The cause of pancreatitis was alcohol abuse in 144 patients, cholelithiasis in nine, endoscopic retrograde cholangiopancreatography (ERCP) in four and unknown in four (*Table 1*).

Computed tomography

A standardized and well characterized method of rapid contrast-enhanced CT has been used since 1981 in patients with clinical suspicion of necrotizing acute pancreatitis[13]. The examination is started without contrast medium to locate the level of the pancreas and evaluate early extrapancreatic findings. These findings are expressed in the first contrast-enhanced CT scan as the extrapancreatic score; oedema in part of the pancreas, oedema of the entire pancreas, peritoneal fluid, perirenal fat oedema, mesenteric fat oedema, pleural effusion and bowel paralysis each give 1 point in a cumulative manner. Thus, a score under 4 suggests mild pancreatitis and the maximum score of 7 the most severe form of disease[8,14].

In patients with an extrapancreatic score of more than 3 and normal renal function, the examination is continued as dynamic contrast-enhanced CT by giving contrast medium as a rapid intravenous bolus in both cubital veins at a dose of 400 mg iodine per kg body-weight. Contrast enhancement of the pancreas at preselected levels (head, body, tail) is measured every 15 s for 2 min and expressed in Hounsfield units. The contrast-enhanced CT scan is then compared with the clinical and laboratory findings to establish the diagnosis and assess the severity of acute pancreatitis.

Treatment

All patients were initially treated with aggressive intravenous fluid resuscitation, intensive monitoring of vital functions and

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Paper accepted 15 October 1995

Table 1 Clinical data

	Site of pancreatic necrosis			
	Right part	Central part	Left part	Entire pancreas
No. of patients	19	5	49	88
Sex ratio (F:M)	1:18	1:4	6:43	9:79
Mean (range) age (years)	42 (21–74)	38 (24–58)	43 (24–64)	40 (19–69)
Mean duration of symptoms (days)	2·2	1·7	2·1	1·7
Relapsing pancreatitis	4	1	9	17
Aetiology				
Alcohol abuse	16	4	45	79
Cholelithiasis	2	0	2	5
Post-ERCP	1	0	1	2
Unknown	0	1	1	2

ERCP, endoscopic retrograde cholangiopancreatography. There were no significant differences between the groups

supportive therapy. In September 1988, in the light of results of a randomized study[15], a radical change in approach to early surgery in necrotizing pancreatitis was made and initial conservative treatment was accepted. Operative intervention was used only when complications, such as infection of the necrosis or deterioration of the clinical condition, occurred despite maximal conservative therapy.

Analysis of contrast-enhanced computed tomography scans

The initial contrast-enhanced CT scans of the 161 patients were analysed by an experienced radiologist (L.K.) without prior knowledge of the clinical outcome or prognostic signs. In the evaluation, special attention was focused on the site of low-contrast enhancement, its extent, the degree of enhancement and any extrapancreatic findings. On the basis of earlier studies, contrast enhancement values below 30 HU were regarded as suggestive of necrosis of the pancreatic tissue[13].

Clinical parameters

Age, sex, aetiology, previous episodes of acute pancreatitis, onset of symptoms, delay between admission and first CT scan, hospital stay, time in the intensive care unit, renal and respiratory insufficiency, total number of operations, infectious complications, late complications such as pseudocyst and diabetes were recorded, as well as mortality, number of positive Ranson's signs, daily CRP levels and other basic laboratory parameters assayed according to the hospital routine. Systemic sepsis confirmed by blood culture, intra-abdominal abscess or infection of the necrosis verified at operation were regarded as infectious complications.

For analysis the patients were grouped in three different ways. The first was according to the extent of pancreatic necrosis, classified as one-third, two-thirds or the entire pancreas involved. The second grouping was according to the site of necrosis, classified in four groups as the entire pancreas, the right part of the pancreas (head or both head and body), the midpart of the pancreas (body) and the left part of the pancreas (tail or both body and tail). Finally, the change of treatment approach from early surgery to initial conservative therapy in September 1988 was considered by dividing records into two time periods: early surgery (patients treated between January 1982 and September 1988) and early conservative treatment (October 1988 to October 1994). The aim of this division was to see whether the change in treatment policy had affected results.

Statistical analysis

Continuous variables were analysed by the two-tailed Mann–Whitney *U* test. Discrete variables were analysed by the χ^2 test and by Fisher's exact test when the number of observations was low. $P < 0·05$ was considered significant.

Results

Typical CT findings of the pancreas in the groups of patients are presented in *Figs 1–4*.

Timing of primary computed tomography

The mean time from onset of symptoms to admission was 1·7 (range 0·2–5·5) days and the mean period in hospital before initial contrast-enhanced CT was 1·2 (range 0·4–5·5) days. Thus, the scans were performed a mean of 2·9 (1·2–6·5) days after the onset of pancreatitis. There were no significant differences between the groups in the timing of CT.

Extent of pancreatic tissue necrosis

There were 46 patients (29 per cent) with one-third of the pancreatic tissue necrotic, 27 (17 per cent) with two-thirds and 88 (55 per cent) with the entire pancreas necrotic.

The relationship between the extent of pancreatic necrosis and clinical outcome is summarized in *Table 2*. Modest correlations were found between the extent of necrosis and the number of days in hospital, the time in intensive care, CRP levels on day 2 after admission and the incidence of diabetes. Some variation was seen in Ranson's early predictive signs, the incidence of renal insufficiency, the incidence of pseudocyst and the extrapancreatic score. Significant differences were found between the groups with one-third and entire pancreatic necrosis in CRP levels, the incidence of respiratory insufficiency, the incidence of infectious complications and the number of operations. Between the groups with one- and two-thirds necrosis there was a significant difference only in extrapancreatic score and in the incidence of respiratory insufficiency. Between the groups with two-thirds and entire pancreatic necrosis there was a significant difference only in the total number of operations. In contrast, the mortality rate was significantly lower in patients with two-thirds necrosis than in those with one-third or the entire pancreas involved.

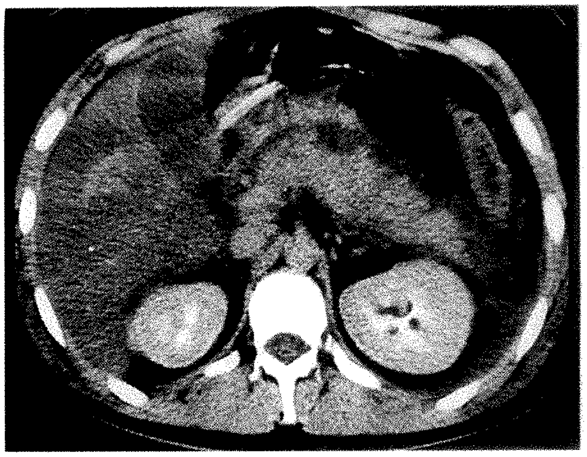

Fig. 1 Contrast-enhanced computed tomography. Contrast enhancement of the entire pancreas of less than 20 HU. Note the peripancreatic changes; the extrapancreatic score is 6

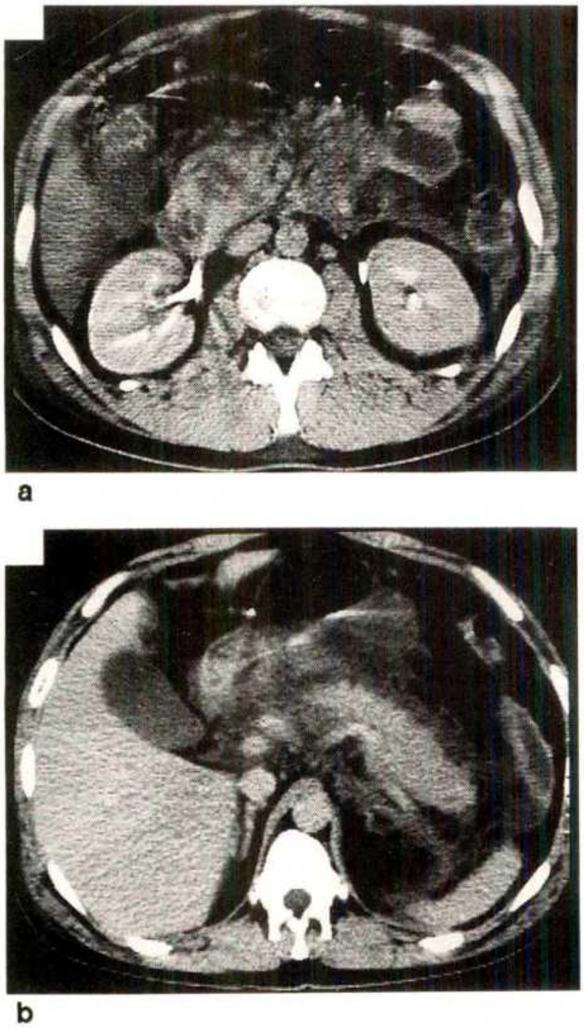

Fig. 2 Contrast-enhanced computed tomography. **a** Contrast enhancement of the pancreatic head of 25 HU. **b** Enhancement of body and tail of more than 35 HU

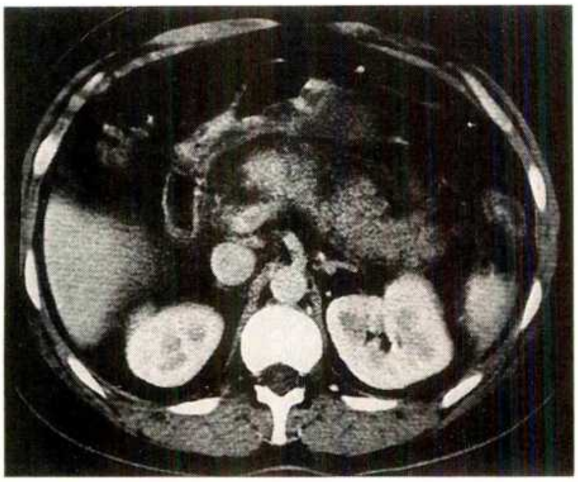

Fig. 3 Contrast-enhanced computed tomography. In the body of the pancreas there is a local necrotic area with low enhancement after the bolus of contrast medium

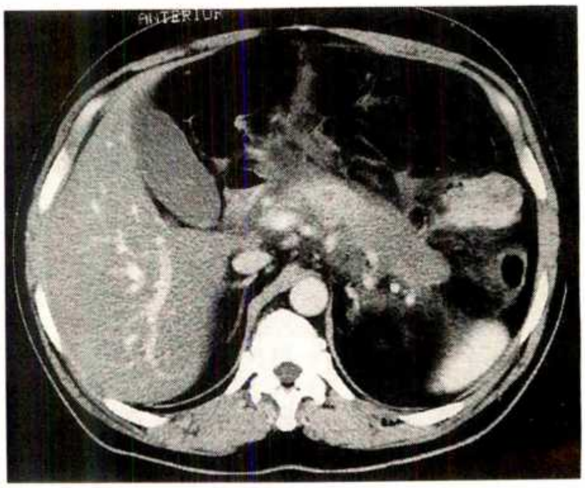

Fig. 4 Contrast-enhanced computed tomography. Left-sided pancreatic necrosis; the enhancement of the head is over 40 HU

Table 2 Extent of pancreatic tissue necrosis and clinical outcome

	Extent of pancreatic necrosis		
	One-third	Two-thirds	Entire pancreas
No. of patients	46	27	88
Mean hospital stay (days)	32	37	42
Mean time in intensive care (days)	13	16	19
Mean no. of positive Ranson's signs	4·2	5·0	4·7
Mean CRP level on day 2 (mg/l)	262*	271	301*
Mean extrapancreatic score	5·7†	6·5†	6·1
No. of deaths	10 (22)‡	1 (4)‡,§	19 (22)§
Frequency of renal insufficiency	8 (17)	3 (11)	21 (24)
Frequency of respiratory insufficiency	18 (39)#	8 (30)¶	47 (53)#,¶
Total no. of operations	21**,††	26**	86††
Frequency of diabetes	5 (11)	6 (22)	23 (26)
Frequency of pseudocyst	11 (24)	8 (30)	15 (17)
Infectious complications	20‡‡	14	52‡‡

Values in parentheses are percentages. CRP, C-reactive protein. Symbols (*,†, etc.) indicate a significant difference ($P < 0.05$) between the two groups labelled

Anatomical distribution of pancreatic tissue necrosis

The entire pancreas was involved in 88 patients (55 per cent), the head and body in five (3 per cent), the head and tail in one (1 per cent), the body and tail in 21 (13 per cent), the head only in 13 (8 per cent), the body only in five (3 per cent) and the tail only in 28 (17 per cent). Thus, the pancreatic head was affected in 107 patients, the body in 119 and the tail in 138.

Results for the distribution of pancreatic tissue necrosis as correlated with clinical findings and outcome are presented in *Table 3*. Significant differences were seen between patients with necrosis of the right part of the pancreas and those with left gland necrosis in extrapancreatic score and incidence of respiratory insufficiency and infectious complications.

Table 3 Site of pancreatic tissue necrosis and outcome

	Site of pancreatic necrosis			
	Right part	Central part	Left part	Entire pancreas
No. of patients	18	5	49	88
Mean hospital stay (days)	42	42	30†	42†
Mean time in intensive care (days)	17	11	13‡	19‡
Mean no. of positive Ranson's signs	5·5	3·0	4·3	4·7
Mean CRP level on admission (mg/l)	54	42	63	61
Mean CRP level on day 2 (mg/l)	282	252	258§	301§
Mean extrapancreatic score	6·3#	6·6	5·7#,¶	6·7¶
Deaths	4 (22)	1 (20)	6 (12)	19 (22)
Frequency of renal insufficiency	4 (22)	2 (40)	5 (10)	21 (24)
Frequency of respiratory insufficiency	12 (67)**	1 (20)	12 (24)**,††	47 (53)††
Total no. of operations	14	3	30‡‡	86‡‡
Frequency of diabetes	2 (11)	1 (20)	6 (12)	22 (25)
Frequency of pseudocyst	6 (33)¶¶	4 (80)¶¶, ***,†††	8 (16)***	13 (15)†††
Infectious complications	15‡‡‡	2	17‡‡‡,§§§	52§§§

Values in parentheses are percentages. CRP, C-reactive protein. Symbols (†,‡, etc.) indicate a significant difference ($P < 0·05$) between the two groups labelled

Table 4 Distribution of patients according to site of pancreatic tissue necrosis and prognostic factors for primary surgery (before September 1988) or conservative therapy (after September 1988)

	Site of pancreatic necrosis			
	Right part	Central part	Left part	Entire pancreas
No. of patients				
Surgery	7	1	21	38
Conservative	11	4	28	50
Mean no. of positive Ranson's signs				
Surgery	5·6	4·0	3·9	4·1
Conservative	5·4	2·8	4·6	5·1
Mean CRP level on day 2 (mg/l)				
Surgery	290	202	215	289
Conservative	248	342	283	311

There were no significant differences between the groups

Between patients with necrosis of the left pancreas and of the entire gland, significant differences were seen in the number of days in hospital, time in the intensive care unit, CRP levels on day 2, extrapancreatic score, incidence of respiratory insufficiency and total number of operations and infectious complications.

Necrosis of the body of the pancreas was often associated with pseudocyst, a late complication; the difference compared with other parts of the pancreas was significant.

The overall clinical outcome was similar for patients with necrosis of the right part of the pancreas and those with the entire gland necrotic.

Effect of the change in primary treatment

There were no significant differences in the distribution of patients among the four anatomical site groups before and after September 1988 (*Table 4*). The effect of site of the necrosis on the clinical outcome was similar in the two periods, but the differences were more striking in patients given early conservative treatment than in those given early surgery. The clinical outcome of these two groups is presented in *Table 5*.

Table 5 Effect of change in the treatment regimen in September 1988 on clinical outcome

	Site of pancreatic necrosis*			
	Right part	Central part	Left part	Entire pancreas
Mean hospital stay (days)				
Surgery	44	57	40	43
Conservative	40	13	25	40
Mean time in intensive care (days)				
Surgery	25	19	18	19
Conservative	17	2	10	19
Deaths				
Surgery	2	1	4	13
Conservative	2	0	2	6
Incidence of renal insufficiency				
Surgery	2	1	3	9
Conservative	2	1	2	12
Incidence of respiratory insufficiency				
Surgery	5	0	8	23
Conservative	7	1	4	24
Infectious complications (total of no. of patients)				
Surgery	5 of 7	1 of 1	11 of 21	30 of 38
Conservative	10 of 11	1 of 4	6 of 28	22 of 50

Discussion

The principal benefit of correct early assessment of severity in acute pancreatitis is that patients who require intensive monitoring and therapy are detected at once. Reliable and reproducible criteria are also needed for choosing comparable patients in clinical trials. Clinical assessment is reliable[3] but tends to be subjective and is therefore of limited value in the early detection of severe acute pancreatitis[2]. Single or multiple biochemical criteria and different scoring systems have been used as prognostic indicators, but none has proved ideal in clinical practice[16].

The authors performed contrast-enhanced CT in about 14 per cent of all patients admitted with acute pancreatitis, the main indication having been clinical suspicion of severe disease. Data for analysis were available from 161 early dynamic CT scans of patients with verified severe acute pancreatitis. In Finland only 8 per cent of all admissions with acute pancreatitis are severe[4,17] and it was not possible to scan all patients for the reasons given earlier. However, the diagnostic accuracy gained by scanning 6 per cent of patients (77 per cent of those with severe pancreatitis) in this study was considered to be adequate.

A marked preponderance of alcohol abuse in the aetiology is typical in Finland, where over 70 per cent of all episodes of pancreatitis are so caused[17]. In the present study this was emphasized because the different treatment of biliary pancreatitis, urgent ERCP or operation makes the arrangement of early contrast-enhanced CT difficult and most CT scans were thus performed on patients with alcoholic pancreatitis. Furthermore, the authors' clinic is specialized in the treatment of severe alcoholic pancreatitis and consequently receives referrals from local hospitals.

The treatment of severe acute pancreatitis has developed considerably[15,18] since January 1982. The main changes are in primary conservative therapy and development of intensive care. The change of treatment policy in September 1988 to a more conservative approach was clearly reflected in mortality rate and clinical outcome. The overall results after primary conservative treatment were significantly better. The main result of this study was seen in both treatment groups. The outcome of patients with left-sided necrosis on early contrast-enhanced CT is better than that of those with necrosis of the pancreatic head or entire pancreas. Comparisons are feasible because the distribution of patients in the two treatment groups was without significant differences.

The main and widely accepted indication for dynamic CT in severe acute pancreatitis is to detect life-threatening local complications and to plan invasive interventions 2–3 weeks after admission[19]. Early contrast-enhanced CT has diminished as a first-line prognostic technique since the treatment regimen is now initially conservative. Clinical evaluation, laboratory parameters such as CRP level and multiple prognostic scoring systems have a satisfactory accuracy. However, in the authors' opinion early contrast-enhanced CT is occasionally needed for early assessment of severe acute pancreatitis. In previous studies from this hospital the accuracy of contrast-enhanced CT in evaluation of acute pancreatitis was demonstrated by comparison with operative and histological findings[10,20]. The investigation has proven to be safe after adequate intravenous fluid resuscitation and when sufficient diuresis is ensured. No harmful effects of the contrast medium on the pancreas have been shown in clinical studies. Early contrast-enhanced CT can be advocated in severe acute pancreatitis when the primary diagnosis is unclear in patients with an atypical presentation or absent laboratory markers[21]. It can also be recommended when accurate prognostic estimation, including the extent and site of pancreatic necrosis as shown in this study, is desired.

Several reports dealing with the prognostic value of CT are difficult to evaluate for a variety of reasons. The timing of CT is inaccurate, being calculated from the time of admission instead of from the onset of pancreatitis. Patients may have their first scan after being in hospital for 1 week or more, CT evaluation varies widely, the analysis may refer to both early and late follow-up CT[11,22], and the course of the disease may change rapidly from serious to a milder form. In this study it was possible to avoid most of those confounding factors, since only the first contrast-enhanced CT scan approximately 3 days after the onset of symptoms was analysed, and well standardized methods for scanning and analysis of contrast-enhanced CT were used.

Balthazar *et al.*[11,23] were able to predict the clinical course of pancreatitis by scoring the degree of pancreatic tissue necrosis; they included the amount of peripancreatic inflammation in their analysis. The peripancreatic changes, which some investigators call peripancreatic inflammation, phlegmon, fluid collection or mixed attenuation collections, are largely dependent on the time lapse between the onset of pancreatitis and CT, and on the intensity of the inflammatory process around the gland. In the present authors' opinion the dependence of this phenomenon on time weakens its value when included in early-phase scoring systems and therefore Balthazar's classification was not considered suitable for the present study.

The most important factor determining outcome in a patient has been shown to be infection of the peripancreatic necrosis[1,16]. Unfortunately, early contrast-enhanced CT does not show which patients will develop this severe complication[9].

The entire pancreas or the pancreatic body and tail were most frequently involved in the necrotic process, the head being relatively resistant to necrosis[24]. This finding is in accord with earlier studies. London *et al.*[22] could find no relationship between necrosis of the pancreatic head or tail and clinical outcome. This may be due to the small number of patients (three) with pancreatic head necrosis in their study.

In the present study, the homogeneous series of patients allowed reliable comparisons between groups. The most striking differences in clinical outcome were between patients with entire pancreatic necrosis and the left part of the pancreas necrotic in hospital stay, time in intensive care, extrapancreatic score, CRP level, incidence of respiratory insufficiency, total number of operations and infectious complications. Similar findings were noted between patients with necrosis of the right part of the pancreas and left-sided involvement. This suggests that necrosis of the pancreatic tail, as detected on early contrast-enhanced CT, may harbour infection less frequently and have a better overall clinical outcome than necrosis of other parts of the pancreas. In groups with necrosis of the right pancreas and entire gland the clinical outcome was similar. However, respiratory insufficiency and infectious complications were more frequent in the former group. This may be explained by the site of the disease process causing obstruction of the duct of Wirsung, so producing a rise in pressure in the acinar cells leading to damage and leakage and activation of proteases. This would also explain the high incidence of late pseudocyst when only the body of the pancreas was involved.

The site of necrosis was a more reliable feature than its extent for predicting the overall outcome in patients suffering from acute necrotizing pancreatitis. This can be explained by the severe course of the disease when necrosis is located proximally and the more favourable outcome for patients with necrosis of the pancreatic tail. The anomalous differences in mortality rate for the groups with pancreatic tissue necrosis of different extent cannot easily be explained.

In conclusion, necrosis of the pancreas is much more dangerous when detected in the head than in the tail and so should alert the clinician to intensive monitoring. When the proximal pancreas alone is affected, the disease is at least as severe as when the entire pancreas is involved. The crude extent of the necrotic area is of less value in prognosis than the anatomical site. In the authors' opinion, this should be taken into account when prospective trials are planned.

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British Journal of Surgery 1996, 83, 930–933

Surgical strategy and management of infected pancreatic necrosis

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Infected pancreatic necrosis and sepsis are the leading causes of death in patients with necrotizing pancreatitis. Between 1986 and 1993, 123 patients with infected pancreatic necrosis were treated; in all cases the infected necrosis extended to the retroperitoneal area. Surgical treatment was performed a mean of 18·5 days after the onset of acute pancreatitis. Operative management consisted of wide-ranging necrosectomy through all the affected area, combined with continuous widespread lavage and suction drainage applied for a mean of 39·5 days, with a median of 6·5 litres of normal saline per day. In 56 cases (46 per cent), another surgical intervention (distal pancreatic resection, splenectomy, cholecystectomy, sphincteroplasty or colonic resection) was also performed. Bacteriological findings revealed mainly enteric bacteria, but *Candida* infection was detected in 21 per cent of patients. The overall hospital mortality rate was 7 per cent (nine patients died). Infected pancreatic necrosis responds well to aggressive surgical treatment, continuous, long-standing lavage and suction drainage, together with supportive therapy combined with adequate antibiotic and antifungal medication.

Acute pancreatitis is an inflammatory process of variable severity ranging from a mild self-limiting form with interstitial oedema of the pancreas to a severe form with extensive pancreatic necrosis and haemorrhage[1–3]. Pancreatic necrosis combined with infection is the leading cause of death in patients with acute pancreatitis. Although aggressive organ-system support has resulted in improved survival in the early stage of the disease, patients continue to die at a later stage from necrotic and septic complications, culminating in multiple-organ failure[4]. The reported mortality rate of these complications ranges from 6 to 80 per cent[5,6]. The severe forms of acute pancreatitis are uncommon, occurring in approximately 5–15 per cent of patients with acute pancreatic inflammation[5,7]. It has recently become apparent that there are three recognizable forms of pancreatic infection according to morphological, clinical and laboratory criteria: infected pancreatic necrosis, pancreatic abscess and infected pseudocyst[8–13]. The mortality rate of patients with infected necrosis is twice that of those with pancreatic abscess, and more than three times that of infected pseudocyst[8,9].

During the 1980s, three main patterns evolved in the surgical management of necrotic and infective complications of acute pancreatitis: (1) 'conventional' treatment, including resection of the involved pancreatic tissue or necrosectomy, followed by drainage; (2) 'lavage' in which necrosectomy is followed by continuous local irrigation or lavage of the involved retroperitoneal area; and (3) 'open abdominal management' (laparostomy), involving resection or necrosectomy followed by various combinations of planned and staged reoperation. Results of the three strategies were reviewed by D'Egidio and Schein[11] in 1991. The mortality rates of documented infected pancreatic necrosis after 'conventional' treatment, 'lavage' and 'open management' were median 42 (range 24–84) per cent, median 18 (range 14–27) per cent and median 21 (range 11–55) per cent respectively.

Since 1986 the authors have adopted wide-ranging necrosectomy and other surgical interventions combined with continuous widespread lavage. This paper analyses the results of this surgical approach to infected pancreatic necrosis.

Patients and methods

Patients

Between 1986 and 1993 a total of 123 patients underwent surgery for infected pancreatic necrosis. During this period, 35 patients with sterile pancreatic necrosis also underwent operation but are excluded from this report. The 123 patients were 95 men and 28 women of mean age 44·4 (range 21–79) years. The aetiology of the underlying acute pancreatitis was alcohol abuse in 80 patients (65 per cent), biliary tract disease in 24 (20 per cent) and hyperlipidaemia in eight (7 per cent); disease was idiopathic in 11 patients (9 per cent). The underlying acute pancreatitis was particularly severe in all patients; the mean number of prognostic signs (Ranson) and mean Acute Physiology And Chronic Health Evaluation (APACHE) II scores were 6·2 (range 4–11) and 15·5 (range 11–31) respectively.

Criteria for the diagnosis of infected pancreatic necrosis included the confirmation of previous or current pancreatitis, clinical evidence and laboratory signs of sepsis, APACHE II score, the retrieval of micro-organisms before and at the time of operation, and pathological examination of tissue after resection of the inflammatory mass. Pancreatic parenchymal necrosis combined with inflammatory complications was generally confirmed by contrast-enhanced computed tomography (CT) and in part by ultrasonography.

Clinical management

After admission and during the early postoperative period, all patients were treated intensively with total parenteral nutrition, adequate fluid resuscitation, cardiac and respiratory monitoring, and antibiotic therapy in accordance with bacteriological findings from the abdomen, blood and bronchial system. In addition, patients with established organ failure, as indicated above, were treated as follows: renal failure by haemodialysis, respiratory failure by adequate mechanical ventilation, circulatory failure by fluid resuscitation and inotropic agents, and hepatic failure and coagulopathy by adequate replacement with fresh frozen plasma and platelets.

Surgical treatment

Surgical treatment was performed a mean of 18·5 (range 8–25) days after the onset of acute pancreatitis. Surgical management

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Presented in part at the Third United European Gastroenterology Week in Oslo, Norway, June 1994 and published in abstract form as *Gut* 1994; 35(Suppl 4): A224
Paper accepted 15 October 1995

was indicated in patients with necrotizing pancreatitis who developed signs of a surgical acute abdomen and septic complications caused by bacterial contamination of the necrosis, combined with persistent organ failure such as pulmonary and/or renal insufficiency. *Table 1* gives the indications for surgery based on clinical factors and the results of laboratory and radiological investigations. In all patients operative management consisted of wide-ranging necrosectomy through the whole affected area, using a bilateral subcostal laparotomy. The abdomen was explored for classification of the extent of pancreatic and extrapancreatic necrosis. Through division of the gastrocolic and duodenocolic ligaments, the extent of necrosis in the head, body and tail of the gland was assessed. For accurate exploration of the retroperitoneum, Kocher's mobilization of the duodenum and mobilization of the right and left colon were performed. The infected necrotizing process was in the right and left retrocolic area in 67 per cent of patients, in one of these and in the left subphrenic area in 21 per cent, and in the retroduodenal and subhepatic area in 12 per cent. Debridement or necrosectomy, either digital or by the careful use of an instrument combined with continuous normal saline lavage, permitted removal of all demarcated devitalized tissue, preserving vital pancreatic tissue[14] and removing the infected necrotic tissue from the whole affected retroperitoneal area. After surgical debridement, meticulous haemostasis and extensive intraoperative lavage with 4–6 litres of normal saline was applied. For postoperative closed continuous local lavage four to 11 large (28–34 Ch) silicone rubber tubes were inserted into all affected areas to lie only in the pancreatic region and retroperitoneal spaces, without any connection with the intra-abdominal region. Some other surgical intervention was also performed in 56 cases (46 per cent).

Continuous lavage and suction drainage was applied for a mean of 39·5 (range 21–90) days, with a median of 6·5 (range 5–15) litres of normal saline per 24 h. In the first few days after operation, the volume of lavage fluid was generally 12–15 litres; this was later reduced depending on the clinical course and on the appearance and quality of the outflowing liquid.

Results

Treatment

A total of 67 patients underwent necrosectomy alone with widespread washing and suction drainage; there were five deaths. In the remaining 56 cases necrosectomy and widespread lavage were combined with additional procedures: distal pancreatic resection and splenectomy ($n = 20$), splenectomy alone ($n = 3$), subtotal pancreatectomy ($n = 3$), colonic resection ($n = 2$), cholecystectomy alone ($n = 24$), cholecystectomy and bile duct drainage ($n = 4$), partial hepatic resection ($n = 1$) and appendicectomy ($n = 2$). Four of these 56 patients died.

Culture of the necrotic tissue, lavage fluid, blood and bronchial system discharge was performed in all 123 patients. Intraoperative samples of necrotic pancreatic tissue indicated bacterial infection in all cases; *Table 2* lists the organisms cultured. Polymicrobial infections were found in 90 per cent of all patients, and a single organism in 10 per cent. Microbiological findings revealed mainly enteric bacteria, but in 26 cases (21 per cent) *Candida* infection was also detected. Fourteen of these patients displayed fungal colonization, while the other 12 had disseminated fungal infection on the basis of the criteria of Burchard *et al.*[15]. There were two deaths in the patients with disseminated fungal infection but none in those with colonization. In both fatal cases, flucytosine was used; when fluconazole was used against disseminated fungal infection, no death occurred.

Complications

Major complications are shown in *Table 3*. Twenty-one patients (17 per cent) had to undergo reoperation; 17 developed a secondary abscess in the area of the original necrotic cavity, massive diffuse local bleeding occurred in three patients and one developed a colonic fistula, which

Table 1 Indications for surgery: clinical factors and results of laboratory and radiological investigations

Clinical factor	No. of patients
Fever (>38·5°C)	123
Leucocytosis ($>15 \times 10^9$/l)	107
Leucopenia ($<2{\cdot}9 \times 10^9$/l)	15
Hypoxaemia	
$P_{a\mathrm{O}_2} < 70$ mmHg	88
$P_{a\mathrm{O}_2} < 60$ mmHg	35
Acute renal failure	5
Positive blood culture	28
Septic shock	12
Prognostic test: APACHE II score	
11–20	92
21–31	31
Ultrasonography	
Necrosis and fluid collection	75
Not diagnostic	48
Computed tomography	
Necrosis, peripancreatic, retroperitoneal inflammatory changes	123

$P_{a\mathrm{O}_2}$, arterial partial pressure of oxygen; APACHE, Acute Physiology And Chronic Health Evaluation

Table 2 Microbiological findings from intraoperative and postoperative specimens of necrotic pancreatic tissue

Polymicrobial infection	111 (90)
Single microbial infection	12 (10)
Organisms isolated (%)	
Enterobacter	54
Pseudomonas	46
Streptococcus	43
Klebsiella	28
Staphylococcus	24
Escherichia coli	16
Anaerobes	16
Acinetobacter	14
Other	9
Candida albicans	21

Values in parentheses are percentages

Table 3 Major complications and outcome after surgical management

Complication	No. of patients	Reoperations	Deaths
Local			
Abscess or necrosis	17	17	7
Fistula			
Pancreatic	16	—	—
Colonic	1	1	—
Bleeding	3	3	1
Systemic			
Respiratory failure	12	—	—
Renal failure	5	—	—
Cardiac insufficiency	3	—	1

was cured by large bowel resection. Only one of the patients undergoing reoperation died, following a procedure for local bleeding. Pancreatic fistula was observed in 16 patients; in eight cases this closed spontaneously but in the remaining eight the fistula became long-standing and of high output. In all eight patients, octreotide therapy (three doses of 0·1 mg each day) combined with total parenteral nutrition for a mean of 13 (range 7–19) days led to complete closure of the fistula[16]. Systemic complications occurred mainly in connection with local complications and reoperation. In 12 patients respiratory failure required mechanical ventilation for over 48 h. Renal and cardiac insufficiency developed in five and three patients respectively.

Nine patients died after operation, to give an overall mortality rate of 7 per cent. The cause of death was bacterial sepsis in five patients, and one each died from bacterial and fungal sepsis, fungal sepsis alone, myocardial infarction and stroke. The median hospital stay of surviving patients was 45 (range 24–95) days.

Discussion

It has become generally accepted[17–19] that bacterial infection of the necrosis is a major prognostic factor in patients with necrotizing pancreatitis. In a prospective clinical study[17], the overall contamination rate of pancreatic tissue necrosis was approximately 40 per cent. Infected necrosis was detected in only 25 per cent of patients after the first week of pancreatitis and in 45 per cent when the duration was 2 weeks. Infected pancreatic necrosis is the most common infectious complication of pancreatitis and also the most severe; it carries the highest mortality rate[6,8,20,21]. As many as 5–10 per cent of all patients with acute pancreatitis may develop this life-threatening complication.

In the authors' experience, criteria for the diagnosis of infected pancreatic necrosis included confirmation of previous or current pancreatitis, clinical evidence of sepsis, determination of the APACHE II score, and the retrieval of micro-organisms before and at the time of operation. Pancreatic parenchymal necrosis combined with inflammatory complications was demonstrated by contrast-enhanced CT; ultrasonography was less helpful.

Bacterial infection is the most important risk factor in necrotizing pancreatitis. Thorough screening for bacterial infection is therefore essential. Fine-needle aspiration is a reliable and safe procedure to detect bacterial contamination of the necrosis[22,23], but retrieval of micro-organisms at the time of operation and in the postoperative period is also important in choosing adequate antibiotics against the bacterial infection. The origin and route of spread of the bacteria that result in pancreatic infection are still unclear. However, it seems likely that they spread by direct transluminal penetration from the colon and/or by spreading along the lymphatics from the gallbladder or colon. It is likely that the virulence of the micro-organisms and the reduced defence capacity of the patient are contributory features[8]. In the present cases the microbiological findings both before, during and after operation showed a high proportion of Gram-negative strains of intestinal origin; polymicrobial infections were almost universal. It was also noteworthy that the prevalence of *Candida* infection was 21 per cent. In all patients *Candida* was isolated in a mixed culture as part of a fungal and bacterial infection. In agreement with various authors[24–26], bacterial sepsis and disseminated fungal infection are not found to be mutually exclusive processes; medications were applied against both organisms. In the present authors' experience with patients with disseminated fungal infection, fluconazole therapy was highly effective and well tolerated[27].

A bilateral subcostal incision was used because this allows wide and safe exploration when extensive infected necrosis is present. The surgical management of patients with infected pancreatic necrosis was directed towards removal of the devitalized pancreatic and extrapancreatic tissue in all affected areas. It seems most important to explore every possibly infected site because ineffective debridement can endanger the recovery of the patient and increase the likelihood of reoperation. It is not necessary to remove every small part of devitalized tissue, because any necrotic or necrotizing tissue is washed out by the lavage fluid later in the postoperative period[10,13,14]. The success of postoperative closed continuous lavage depends on the number and size of the drainage tubes[28,29]. Four to 11 large silicone tubes were generally inserted to drain all affected places. As the infected necrotic process can extend into pancreatic and extrapancreatic areas, other surgical interventions may also be required. This explains why in 46 per cent of patients necrosectomy and continuous lavage were combined with other surgical interventions.

Reoperation was necessary in 21 patients (17 per cent), mainly as a consequence of residual abscesses. The overall mortality rate was 7 per cent, which demonstrates the value of the strategy and management in patients with infected pancreatic necrosis. We attribute the improved survival rate to adequate surgical debridement combined with continuous widespread lavage and suction drainge of all affected areas. A large volume of saline solution for continuous lavage through multiple drainage tubes is a safe and atraumatic procedure that can eliminate infected necrotic tissue. Effective surgical treatment together with supportive therapy, combined with adequate antibiotic and antifungal medication, can give good results in patients with infected pancreatic necrosis.

Acknowledgements

This work was supported by a grant from OTKA I/3, no. 2727.

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British Journal of Surgery 1996, 83, 934–937

Operative strategies in pancreatic trauma

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Pancreatic injuries are relatively uncommon and the choice of an appropriate operative procedure can be difficult. Operations for pancreatic trauma from January 1990 to June 1993 have been reviewed. Fifty-one patients were studied; 13 had blunt trauma, 17 gunshot wounds and 21 stab wounds. The distribution of injuries was: pancreatic head (17), body (15) and tail (19). Most patients had associated injuries of surrounding organs. Operations performed included pancreatoduodenectomy (seven), distal pancreatectomy (seven) and external drainage (35). Five patients (10 per cent) died: two from haemorrhage, one from an acute subdural haematoma and two from multiple organ failure. Ten patients (20 per cent) developed a pancreatic fistula, four following blunt trauma, four after gunshot wounds and two with stab wounds; all but one had undergone drainage procedures. Stab wounds were associated with a low incidence of duct injury and external drainage was usually satisfactory. After blunt trauma and gunshot wounds, duct injuries were common and easily missed; careful exploration by an experienced surgeon is essential. In appropriately selected patients, pancreatic resection can be performed with good result.

Injuries of the pancreas are relatively uncommon and in many cases occur in association with major trauma to other organs. It is these associated injuries that account for the majority of deaths in patients with pancreatic trauma[1–4]. Consequently, large institutional series collected over several decades[1–3,5] may not be relevant to current management of pancreatic trauma because of changes in the proportion of blunt *versus* penetrating trauma, advances in prehospital care and transportation of trauma victims, better resuscitation and intensive care facilities, and improved management of associated injuries. In this study, therefore, the authors' recent experience of pancreatic trauma specifically was reviewed, and the significance of the mechanism of injury and its influence on operative management of pancreatic injuries was evaluated.

Patients and methods

Records of patients undergoing laparotomy for abdominal trauma between January 1990 and June 1993 were examined to identify cases of pancreatic trauma. Demographic data, mechanism of injury and operative findings were recorded, together with the operative procedure performed, postoperative course and complications. A modified form of the Lucas classification[6] was used to grade the severity of pancreatic injury (*Table 1*). Statistical analysis was performed using non-parametric methods (Mann–Whitney *U*, χ^2 and Fisher's exact tests as appropriate).

Management

Following initial assessment and resuscitation, patients with evidence of ongoing intra-abdominal haemorrhage or hollow viscus injury underwent laparotomy. All patients in whom a pancreatic injury was suspected underwent early laparotomy; however, in most cases the decision to operate was made on evidence of haemorrhage, peritonism or increasing abdominal tenderness. In only one patient was operation carried out more than 48 h after injury. Preoperative investigations included haemoglobin estimation and plain radiography as appropriate. Serum amylase was not measured routinely and ultrasonography and computed tomography were not performed. Most laparotomies were performed by surgical registrars. Consultants performed or assisted at operation on critically injured patients, or attended when requested by the registrar. All pancreatic resections were performed by a consultant.

Table 1 Modified Lucas classification of pancreatic trauma

Class 1	Contusion or peripheral laceration with minimal parenchymal damage. Main pancreatic duct intact
Class 2	Major laceration, perforation or transection of body or tail with or without duct injury
Class 3	Severe crush, perforation or transection of the pancreatic head with or without duct injury
Class 4	Combined pancreaticoduodenal injury:
a	Minor pancreatic injury
b	Severe pancreatic injury with duct disruption

Results

Between January 1990 and June 1993, 101 717 patients were seen in the Trauma Unit of this hospital. Of these, 1363 underwent laparotomy for abdominal trauma. Fifty-one patients had pancreatic injuries confirmed at operation (3·7 per cent of laparotomies); 13 were caused by blunt trauma (nine motor vehicle accidents and four assaults), 17 were gunshot wounds and 21 stab wounds. There were 45 men and six women; their ages ranged from 14 to 46 (mean 26·9, median 23) years.

Mechanism of injury and operative findings

The grade and distribution of pancreatic injuries are shown in *Table 2*. Injuries resulting from blunt trauma and gunshot wounds predominantly involved the pancreatic head and body, while most stab wounds affected the tail. Major parenchymal injuries (classes 2 and 3) and those involving the duodenum (class 4) were common following blunt trauma and gunshot wounds but seldom occurred in stab wounds. Injuries to other organs were common in all groups (*Table 3*). Hollow viscera were injured more

Paper accepted 5 November 1995

Table 2 Class, distribution and mechanism of 51 pancreatic injuries

	Class of injury*					Anatomical distribution		
	1	2	3	4a	4b	Head	Body	Tail
Blunt	6	3	0	2	2	6	5	2
Gunshot	7	2	2	2	4	8	5	4
Stab	18	1	0	1	1	3	5	13
Total	31	6	2	5	7	17	15	19

*Modified Lucas classification

Table 3 Associated injuries

	Mechanism of injury		
	Blunt ($n = 13$)	Gunshot ($n = 17$)	Stab ($n = 21$)
Duodenum	4	7	1
Liver	5	10	7
Gallbladder	0	3	0
Common bile duct	0	1	1
Portal vein	1	0	1
Superior mesenteric vein	1	2	0
Vena cava	1	6	2
Spleen	3	0	3
Splenic vessels	0	2	0
Diaphragm	0	0	7
Stomach	0	8	14
Colon	0	3	2
Mesocolon	1	0	1
Small bowel	2	2	1
Kidney	1	2	0
Renal artery	0	1	1
Ureter	0	1	0
Adrenal vein	0	2	0
Aorta	0	1	0

frequently in penetrating than in blunt trauma. Only four patients had isolated pancreatic injuries (three to the body and one to the head), all following blunt trauma.

Operative procedures

Major pancreaticoduodenal injuries were found in seven patients and were managed by pancreatoduodenectomy (four pylorus-preserving and three Whipple procedures). Pylorus-preserving resections were performed in two patients with blunt trauma: one patient had a complete avulsion of the duodenal 'C loop' from the head of the pancreas, with disruption of the ampulla of Vater; the other had extensive destruction of the pancreatic head and multiple seromuscular ruptures of the second and third parts of the duodenum. The five patients who underwent pancreatoduodenectomy for gunshot wounds all had significant injuries to adjacent organs in addition to major disruption of the pancreatic head and duodenum. In one patient, the bullet had passed through the distal stomach and in another two the duodenum was injured within 3 cm of the pylorus; these three patients underwent classical Whipple resections. The remaining two patients had more distal duodenal injuries and were managed by pylorus-preserving resection.

Complete transection of the body of the pancreas was found in two patients and injury of the main pancreatic duct was suspected in a further four; all six patients underwent distal pancreatectomy, three with and three without splenectomy. A further patient with a gunshot wound to the splenic vessels and pancreas (without apparent duct injury) underwent distal pancreatectomy and splenectomy. Four patients with exsanguinating haemorrhage from associated liver injuries underwent therapeutic perihepatic packing[7]: in one, a pancreatic laceration and a laceration of the portal vein were sutured and the subhepatic space was packed for 48 h, before placement of an external drain; in another, a drain was placed for a pancreatic contusion; two patients died before their pancreatic injuries could be addressed. The remaining 33 patients were managed by external drainage of the pancreatic injury. Closed suction or corrugated drains were used according to the surgeon's preference. The pancreatic wound was not sutured except where necessary for haemostasis. Fibrin glue products were not used and no patient received somatostatin analogues.

Outcome

Five patients died, four after blunt trauma (pedestrians in road accidents) and one from a gunshot wound, giving a mortality rate of 10 per cent. The mortality rate was not related to the grade of pancreatic injury but was higher after blunt trauma than penetrating trauma (*Table 4*). All five patients who died had other major upper abdominal injuries and were shocked before and during laparotomy. The four patients with blunt trauma all required therapeutic packing for liver injuries and three also underwent splenectomy. Two patients died on the operating table from uncontrollable haemorrhage from major vascular injuries and a third died during emergency craniotomy for an acute subdural haematoma, having undergone liver packing and external drainage for a contused pancreas. The fourth patient died from multiple organ failure. One patient who died after a gunshot wound had gross destruction of the pancreatic head (class 3 injury), together with injuries of the liver, stomach, vena cava and superior mesenteric vein. He underwent a Whipple resection but died 2 days later from multiple organ failure.

Hospital stay in the 46 survivors ranged from 4 to 47 (mean 16·5, median 10) days and was longer for blunt trauma and gunshot wounds than for stab wounds (median stay 20, 23 and 8 days respectively; $P < 0{\cdot}01$). There was no significant difference in hospital stay for patients with blunt trauma (median stay with resection 19 days, with drainage 23 days) compared with those who had gunshot wounds (median stay 20 and 26 days respectively). Postoperative complications tended to occur more frequently in patients with a higher grade of

Table 4 Mortality and morbidity rates

	Class of injury*					Mechanism of injury		
	1	2	3	4a	4b	Blunt	Gunshot	Stab
No. of patients	31	6	2	5	7	13	17	21
Deaths	3	1	1	0	0	4	1	0
Complications	11	4	1	4	6	7	11	6

*Modified Lucas classification

Table 5 Complications in 46 patients* with pancreatic injuries (all causes)

Abdominal	No. of patients	Systemic	No. of patients
Pancreatic fistula	10	ARDS	3
Bile leak	2	Atelectasis	3
Intra-abdominal abscess	2	Renal failure	2
Postoperative haemorrhage	2	Pneumonia	1
Duodenal ileus	2	Pleural effusion	1
Pancreatitis	1	Pulmonary embolus	1
Biliary fistula	1		
Duodenal fistula	1		
Wound abscess	1		
Late bile duct stricture	1		

*Early deaths were excluded. ARDS, adult respiratory distress syndrome

pancreatic injury (*Table 4*). Complications were more common following blunt trauma or gunshot wounds than after stab wounds (*Table 4*; $P < 0.02$).

Abdominal and systemic complications are listed in *Table 5*. Ten patients (20 per cent) developed a pancreatic fistula. The development of this complication was not predicted by the site or severity of injury as assessed at operation. Fistula was more common in patients who had undergone laparotomy for blunt trauma (four of nine survivors) or gunshot wounds (four of 16) than for stab wounds (two of 21). In cases of blunt trauma or gunshot wounds, postoperative pancreatic fistula occurred only in patients who had undergone drainage procedures rather than pancreatic resection. Of the two patients who developed a pancreatic fistula from stab wounds, one had undergone external drainage. The patient who developed a pancreatic fistula following resection (distal pancreatectomy) had presented to hospital more than 48 h after being stabbed and had fat necrosis around the pancreatic tail. There was no correlation between fistula formation and the type of drain used.

The subsequent morbidity from the pancreatic fistula was not affected by the site of the injury. Six of the ten fistulas settled with conservative management; parenteral nutrition was required in four patients. Endoscopic sphincterotomy was performed in one patient, one had a lateral pancreaticojejunostomy (Puestow procedure) and two underwent pancreatic resection (of whom one had a recurrent fistula, managed by parenteral nutrition). Median hospital stay for patients with a pancreatic fistula was 30 days compared with 16 days for those with blunt or gunshot injuries who did not develop this complication and 8 days following stab wounds.

Other complications showed no association with the type of operation performed (pancreatic resection *versus* drainage). There were no cases of post-traumatic pancreatic pseudocyst in this series, although the authors reported this complication in an earlier series[8]. In general, complications tended to be less frequent in patients with stab wounds (*Table 4*).

Discussion

Pancreatic injuries may be complex and can present formidable technical challenges, even to the experienced surgeon. In addition, injuries to other abdominal organs, including major vessels, liver, spleen and hollow viscera, may be present. Most deaths in pancreatic trauma are attributable to these associated injuries[4]. In this series, three of the five patients who died had relatively minor pancreatic trauma. The authors' priorities, therefore, in operations for life-threatening abdominal trauma which includes a pancreatic injury, are control of haemorrhage, minimizing contamination from hollow visceral injuries and management of liver and splenic injuries. Thereafter, the patient's general condition is the principal factor determining the choice of procedure for management of the pancreatic injury. All of the patients who survived resection in this series were haemodynamically stable at operation, whereas the patient who died following pancreatoduodenectomy had been shocked throughout the procedure. Unstable patients are probably best served by a 'damage control' procedure, transfer to the intensive care unit and stabilization before attempting definitive surgery[9,10]. This is an established strategy for liver[7] and other major abdominal trauma[11,12] and was used successfully in one patient in this series with a stab wound of the pancreatic head, portal vein and common bile duct, in whom the pancreatic injury healed, but a late bile duct stricture required reconstructive surgery.

In stable patients, an appropriate procedure must be chosen to minimize the risk of fistula formation. Recommendations have previously been based on assessment and grading of the injury according to the Lucas classification[6,13]. In this series, however, fistulas occurred mainly in patients assessed as having grade 1 injuries, i.e. in whom pancreatic duct injury was not recognized. Detecting a duct injury in a stab wound of the pancreas is easier than in blunt or gunshot injuries, where the duct may be obscured by surrounding contused and necrotic tissue, and may explain why fistulas occurred more commonly in the latter patients. Intraoperative pancreatography has been advocated for the diagnosis of duct injuries but the reported detection rate is similar to that achieved by surgical exploration alone[14].

A variety of procedures for internal drainage and/or defunctioning of the pancreas have been advocated as an alternative to resection[13]. The present authors consider these procedures inappropriate as they are time consuming and hazardous in the unstable patient and because internal drainage as a primary procedure involves the construction of an anastomosis to acutely injured pancreatic tissue. Consequently, significant morbidity and mortality rates have been reported for these procedures: of 58 patients[1-3] managed by internal drainage, 11 died and 11 developed a pancreatic fistula. Results of duodenal diverticulization have been reported in 58 patients[15,16]: nine patients died and 14 developed a fistula (seven pancreatic, seven duodenal). Pyloric exclusion[17] was performed in 75 patients, of whom 14 died and nine developed a pancreatic fistula. The authors believe that the reduced morbidity which Berni *et al.*[14] attributed to the use of intraoperative pancreatography is more likely to reflect their increasing use of pancreatic resection and abandonment of internal drainage procedures for pancreatic trauma. The choice of operative procedure should therefore be either resection or external drainage of the injured pancreas.

Based on the results of this study, the following management strategy is proposed for haemodynamically stable patients with pancreatic injuries:

1. Minor contusions, lacerations or gunshot wounds of the upper or lower border of the body/tail of the pancreas (i.e. remote from the main pancreatic duct) or stab wounds without visible duct involvement should be managed by external drainage.
2. Major contusions and lacerations of the body/tail of the pancreas, gunshot wounds in the region of the pancreatic duct in the body/tail and stab wounds of the body/tail with visible duct involvement should be treated by distal pancreatectomy.
3. Stab wounds, gunshot wounds and minor contusions of the head of the pancreas, without devitalization of pancreatic tissue, should be managed by external drainage provided that any associated duodenal injury is amenable to simple repair.
4. Pancreatoduodenectomy as a primary procedure should be restricted to stabilized patients with disruption of the ampulla of Vater or major devitalizing injuries of the pancreatic head and duodenum. Injuries of this severity occur after blunt trauma or gunshot wounds but are uncommon with stab wounds.

By using this classification, the authors believe that patients can be managed either by simple external drainage or pancreatic resection with good result. Internal drainage or complex defunctioning procedures can be avoided without increasing morbidity and have no place in the current emergency management of pancreatic injuries.

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British Journal of Surgery 1996, 83, 938–941

Randomized comparison of pulmonary function after the 'French' and 'American' techniques of laparoscopic cholecystectomy

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The 'French' and 'American' techniques of laparoscopic cholecystectomy, which differ in the position of the surgeon and ports, have not been compared directly. The authors' hypothesis was that the 'French' technique results in better postoperative pulmonary function than the 'American' technique. Patients undergoing elective cholecystectomy were randomized, 25 patients to have the 'French' method and 24 the 'American' method. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured before operation, and 6, 24 and 48 h after surgery. Postoperative pain and fatigue were also measured. Both FVC and FEV1 at 6 h, 24 h and 48 h after operation were significantly less in the 'American' group (FVC at 24 h: 71 *versus* 86 per cent of preoperative value; $P = 0{\cdot}001$, Student's *t* test; 95 per cent confidence interval 7–24). Two cases of atelectasis occurred in the 'American' group and none in the 'French' group. Differences in access to Calot's triangle were also noted. One patient in the 'French' group sustained a diathermy injury of the duodenum, related to defective equipment. It is concluded that the 'French' method leads to less impairment of pulmonary function.

At present, there are two main techniques of laparoscopic cholecystectomy: the 'French' technique in which the surgeon stands between the patient's legs, and the 'American' technique in which the surgeon stands to the left of the patient[1,2]. The former approach is common in continental Europe but the latter is the dominant technique elsewhere. These two methods have been considered to be practically the same. However, in reality, there are fundamental differences in port placement and approach to Calot's triangle that make the two procedures distinctive. For optimal performance, different types of instruments and training in each method are required.

This paper examines the different approaches and limitations of each method. Based on the knowledge that lower placement of incisions in the abdomen leads to better postoperative pulmonary function, the authors' main hypothesis was that the 'French' technique, in which the ports are inserted mainly in the mid-abdominal region, results in better postoperative pulmonary function than the 'American' technique, in which the ports are concentrated in the right hypochondrium.

Patients and methods

Patient selection and study design

Between April and November 1994, patients who were admitted to one surgical ward for elective laparoscopic cholecystectomy were recruited into the study. The inclusion criterion was symptomatic cholelithiasis (biliary colic with cholelithiasis proved ultrasonographically). Patients with associated choledocholithiasis were also recruited after successful extraction of stones by endoscopic techniques (endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy). Patients were excluded if they had acute cholecystitis, previous major abdominal surgery, were pregnant, or if the patient refused to participate in the trial.

Eligible patients were randomized to either the 'French' or 'American' technique on the morning of operation. Stratified randomization was achieved by means of sealed envelopes. The patients were stratified into: (1) those with chronic lung disease; (2) those with significant co-morbid disease (ischaemic heart disease, cardiac insufficiency, renal failure, liver cirrhosis, etc.); (3) those who were overweight or obese based on body mass index[3] (see *Table 1*); and (4) a normal group with none of the above conditions that may affect pulmonary function. Randomization was in blocks of four to 16 for each group depending on the expected number of patients in that group.

Paper accepted 20 September 1995

Table 1 Demographic data and preoperative status

	'French' technique ($n = 23$)	'American' technique ($n = 22$)	*P*
Mean(s.d.) age (years)	48(13)	57(12)	0·023‡
Sex (M:F)	5:18	6:16	n.s.§
BMI (*n*)			
Normal (BMI < 25)	9	10	n.s.§
Overweight (BMI ≥ 25, < 30)	5	6	
Obese (BMI ≥ 30, < 40)	8	6	
Morbidly obese (BMI ≥ 40)	1	0	
ASA grade			
I	9	5	n.s.§
II	14	16	
III	0	1	
Cardiac impairment* (*n*)	2	2	n.s.¶
Chronic lung disease† (*n*)	4	3	n.s.¶
Smoking history (*n*)			
Non smoker	18	19	n.s.¶
< 20 per day	4	1	
≥ 20, < 40 per day	1	2	
Indication for operation (*n*)			
Biliary colic	22	18	n.s.¶
Subacute/chronic cholecystitis	1	2	
Choledocholithiasis	0	2	
Mean(s.d.) preoperative FVC (litres)	2·86(0·69)	2·86(0·78)	n.s.‡
Mean(s.d.) preoperative FEV1 (litres)	2·52(0·70)	2·50(0·75)	n.s.‡

*All had ischaemic heart disease with compensated cardioinsufficiency. †Characterized by shortness of breath on effort and forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) below 70 per cent of expected values. BMI, body mass index; ASA, American Society of Anesthesiologists; n.s., not significant. ‡Student's two-tailed *t* test; §χ^2 test; ¶Fisher's exact test

Laparoscopic cholecystectomy

All procedures were performed under general anaesthesia that was induced with intravenous propofol 2 mg/kg, followed by atracurium 0·5 mg/kg to facilitate intubation. Anaesthesia was maintained by isoflurane 1 per cent and nitrous oxide 50 per cent. Ventilation was adjusted to maintain end-tidal carbon dioxide between 35 and 40 mmHg. Additional doses of atracurium were given to maintain one or two responses to train-of-four stimulation. Intravenous fentanyl 0·1 mg/kg was given if there were signs of inadequate analgesia. At the end of surgery, the anaesthesia was reversed with neostigmine 0·05 mg/kg, atropine 0·02 mg/kg and 100 per cent oxygen. For postoperative analgesia, intravenous tramadol was given when the patient complained of pain. No local anaesthetic agent was infiltrated into the wound at any time to any patient.

For the 'French' method[4], a 10-mm cannula with a blunt trocar was inserted below the umbilicus for the laparoscope using the open method of introduction. After carbon dioxide insufflation up to 14 mmHg, a 5-mm port was inserted in the epigastrium for the suction–irrigation device, followed by two 10-mm ports to the left and right side of the mid-abdomen at about the level of the umbilicus. The right port was for the gallbladder grasper and the left port for the electrocautery hook dissector. The gallbladder was extracted through the right mid-abdominal wound. This is the technique normally used in this hospital.

For the 'American' technique[2], the surgeon stands on the left of the patient. The subumbilical port was inserted as described above, then a 10-mm port was inserted in the epigastrium to be used for dissection and clipping of the cystic duct. A 5-mm port was inserted in the subcostal region along the mid-clavicular line for retraction of Hartmann's pouch, and another 5-mm port in the subcostal region along the anterior axillary line for retraction of the gallbladder fundus. The gallbladder was extracted through the epigastric port.

Quality assurance

Both procedures were either performed or closely supervised by surgeons with experience of more than 50 cases in each of the techniques. Since the 'French' technique is the usual practice of this hospital, the operators were all familiar with this method. The 'American' operations were performed or supervised by the first author who has been trained in this method. Efforts were made not to allow the operation to be unnecessarily prolonged for more than 90 min. The duration of operation, significant intraoperative incidents (e.g. stone spillage, stone loss, more than usual haemorrhage) and the need for extension of the wound for gallbladder extraction were recorded prospectively.

Respiratory function

The primary endpoint was the postoperative pulmonary function. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured before operation, and 6, 24 and 48 h after surgery using the Vicatest P2 digital spirometer (PPG Hellige, Dortmund, Germany). All measurements were obtained at the bedside in the sitting position and in accordance with the recommendations of the American Thoracic Society[5]. At each session, the best of five attempts was printed by the machine. Postoperative pulmonary function was expressed as a percentage of the preoperative value. The patients were also examined clinically for signs of atelectasis and pneumonia.

Postoperative recovery

Postoperative pain, fatigue and recovery were also measured 6, 24 and 48 h after operation. Intensity of pain was documented both by a visual analogue scale ranging from zero (no pain) to 100 (intolerable pain), and by the type and amount of analgesia requested by the patient. Depending on the severity of pain, either intravenous tramadol or enteral ibuprofen was given. Postoperative fatigue was also estimated with a visual analogue scale in which zero signified fitness, 40 mild tiredness, 70 tiredness and 100 exhaustion. Postoperative recovery was assessed by the number of days before the patient could resume fluid and normal diet intake, and to become mobile.

Sample size calculations and statistical analysis

Sample size calculation was based on the aim of detecting a difference of at least one standard deviation (about 15–20 per cent of preoperative value from previous studies[6,7]) in postoperative pulmonary function, in order that the difference may have clinical significance. It was calculated that for $\alpha = 0{\cdot}05$ (two-tailed) and statistical power $= 0{\cdot}9$, at least 22 patients in each group were needed.

Normally distributed numerical data were expressed as mean(s.d.) and tested with Student's *t* test. Skewed distributions were given as median (interquartile range) and tested with the Mann–Whitney *U* test. Categorical data were tested with the χ^2 or Fisher's exact test if the values were small. A *P* value less than 0·05 was considered significant.

Results

During the study period, 49 eligible patients were recruited; 25 were randomized to the 'French' method and 24 to the 'American' method. Two patients in each group were eventually excluded. One patient undergoing the 'French' method sustained thermal injury to the duodenum from a defective, poorly insulated hook dissector. Intraoperative gastroscopic assessment of the duodenal damage and laparoscopic suturing (requiring two additional ports) of the burnt area resulted in a 180-min procedure. One patient undergoing the 'American' technique had to undergo conversion to open surgery because a 2-cm stone was lost in the peritoneal cavity. One patient from each group was admitted to the intensive care unit because of cardiac instability and the protocol for postoperative pulmonary function measurement could not be followed.

The demographic data and baseline preoperative status are shown in *Table 1*. By chance of randomization, the patients in the 'American' group were slightly older. However, the other baseline parameters were similar. All procedures started about 15 min after intubation. The mean(s.d.) duration of operation was 67(17) min and 69(19) min for the 'French' and 'American' techniques respectively. No intraoperative cholangiography was performed. Minor intraoperative incidents, such as gallbladder perforation with bile and stone spillage or controllable bleeding, occurred in about one-quarter of patients in both groups. Wound extension for gallbladder extraction was required for eight patients in the 'French' group and 11 in the 'American' group (*P* not significant,

Table 2 Postoperative lung function tests

	'French' technique (*n* = 23)	'American' technique (*n* = 22)	*P**	95 per cent confidence interval
FVC at 6 h	71(13)	60(17)	0·016	2–20
FEV1 at 6 h	74(14)	58(15)	0·001	6–24
FVC at 24 h	86(10)	71(18)	0·001	7–24
FEV1 at 24 h	90(15)	72(18)	0·001	7–27
FVC at 48 h	91(12)	76(16)	0·001	7–24
FEV1 at 48 h	96(16)	79(15)	0·001	7–26

Values are mean(s.d.) percentage of preoperative value. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s. *Two-tailed Student's *t* test

Table 3 Postoperative pain intensity, use of analgesia and location of pain

	'French' technique ($n = 23$)	'American' technique ($n = 22$)	P
Pain intensity*			
At 6 h, lying	38 (24–46)	38 (20–44)	n.s.§
At 6 h, sitting	55 (36–64)	55 (39–71)	n.s.§
At 24 h, lying	22 (5–32)	28 (13–37)	n.s.§
At 24 h, sitting	32 (19–75)	43 (30–54)	n.s.§
At 48 h, lying	5 (0–15)	21 (0–28)	0·034§
At 48 h, sitting	20 (6–28)	36 (18–47)	0·021§
Analgesic medication			
Intravenous opiates†			
No. of patients	10	13	n.s.¶
Median (i.q.r.) dose (mg)	25 (5–40)	25 (8–40)	n.s.§
Enteral analgesia‡			
No. of patients	10	12	n.s.¶
Median (i.q.r.) dose (mg)	450 (300–1350)	600 (300–1500)	n.s.§
Main location of pain (n)			
Epigastric wound	1	12	<0·001**
Umbilical wound	7	1	
Right abdominal wound	12	2	
Right hypochondrial pain	3	7	
Shoulder pain (n)			
Right	8	6	n.s.**
Left	2	0	

*Values are median (interquartile range (i.q.r.)) score measured on a visual analogue scale from zero to 100 (0, no pain; 100, intolerable pain). †Intravenous tramadol was given for severe pain; expressed in morphine equivalents. ‡Ibuprofen given orally or as a suppository. n.s., Not significant. §Mann–Whitney U test; ¶χ^2 test; **Fisher's exact test

χ^2 square test). In both groups, patients with extended wounds had pain scores and pulmonary function which were not significantly different from those in patients whose wounds were not extended.

Postoperative pulmonary function was poorer in the 'American' group (*Table 2*). There were two cases of atelectasis (low-grade fever, basal crepitations) in this group, which resolved after the second day. No patient in the 'French' group developed atelectasis. None of the patients in either group developed pneumonia that required active treatment.

Mean postoperative pain intensity on the visual analogue scale showed a difference only at 48 h (*Table 3*). There was no difference in analgesia usage. However, the pain was mainly mid-abdominal in the 'French' group, and mainly upper abdominal in the 'American' group ($P < 0{\cdot}001$, Fisher's exact test). The incidence of shoulder pain was similar.

Mean postoperative fatigue on the visual analogue scale was not statistically different between the 'French' and 'American' groups (6 h: 48 *versus* 57; 24 h: 25 *versus* 33; 48 h: 24 *versus* 24). Most of the patients in both groups could drink on the day of operation and they became mobile and had solid food on the first day after operation.

Discussion

The 'French' and 'American' techniques of laparoscopic cholecystectomy developed out of the surgeons' personal preferences and have not been compared in a scientific way. Vitale *et al.*[8], who looked at the return to professional and home activities after each method, concluded that cultural norms played a dominant role in these endpoints. The present authors had the unique opportunity to compare the two methods in the same setting because surgeons who were experienced in each of the techniques were brought together to work for 1 year. Since the placement of ports was different, postoperative pulmonary function was chosen to be the objective primary endpoint.

Abdominal surgery leads to restrictive impairment of pulmonary function[9,10]. Vital capacity, FEV1 and functional residual capacity may decrease 40–60 per cent from preoperative levels after open upper abdominal surgery. Comparative studies both between laparoscopic and open cholecystectomy[6,11], and between laparoscopic and minilaparotomy cholecystectomy[6,7], have shown better postoperative pulmonary function with the laparoscopic approach. Pulmonary function after laparoscopic cholecystectomy was shown to be decreased to about 65–74 per cent of preoperative value. The authors did not specify the technique of laparoscopic cholecystectomy but, based on the origin of these papers, it is most likely that the 'American' method was used.

The cause of postoperative pulmonary dysfunction is multifactorial. However, with similar techniques of anaesthesia, duration of surgery and amount of surgical trauma in this study, the main factors were pain and diaphragmatic dysfunction. Diaphragmatic dysfunction, even in the absence of pain, has been well documented after open surgery[12]. It is speculated that the upward traction in the 'American' technique may have led to more diaphragmatic splinting. However, in a recent uncontrolled study, Couture *et al.*[13] showed that diaphragmatic function was less impaired during laparoscopic cholecystectomy than in open surgery.

Pain appears to be the main factor that leads to the altered breathing pattern (rapid and shallow), and abdominal and lower intercostal muscle reflex spasm that contribute to small airway closure, intrapulmonary shunting and hypoxaemia[14,15]. Since the intensities of pain on the visual analogue scale were similar, the difference in postoperative pulmonary functions between the 'French' and the 'American' techniques most likely resulted from the different locations of the pain. Location of the incision and thus the site of pain has been shown to significantly affect pulmonary function[16]. The higher location of pain with the 'American' technique, related to the concentration of the ports in the epigastrium and subcostal region and extraction of the gallbladder via the epigastric wound, conceivably affected the function of the respiratory muscles more. The authors do realise that some surgeons using the 'American' technique remove the gallbladder through the umbilical port. Perhaps use of the umbilicus as the extraction point may improve pulmonary function, especially when a significant proportion of epigastric wounds have to be extended for gallbladder extraction, although the authors found no effect of wound extension on pulmonary function. The slightly older sample in the 'American' group may theoretically bias the results of pulmonary function tests, but it is unlikely to do so to a significant degree since the other preoperative parameters were similar for both groups.

The sample size was too small to determine the clinical impact of reduced postoperative pulmonary function in terms of chest infection. However, it is noteworthy that atelectasis occurred in two patients in the 'American' group. For a common operation like laparoscopic cholecystectomy, any improvement in respiratory function is likely to benefit a significant number of patients, especially those at higher risk of postoperative pulmonary infection (e.g. patients with chronic lung disease, cardiac insufficiency, obesity).

Certain fundamental differences between the two methods have been noted by the authors. The lower placement of ports in the 'French' technique results in an acute-angled approach to the gallbladder. The advantage is that it allows easy access to both the cephalic and caudal surfaces of Calot's triangle. Also, with one grasper retracting the gallbladder laterally and the suction–irrigator device retracting the liver, Calot's triangle is splayed open. Both these factors facilitated safe dissection of this key region. Hunter[17] suggested that emphasis on lateral retraction may account for the lower incidence of common bile duct injuries reported in Europe (0·33 per cent) compared with the USA (0·5–2·7 per cent) during the early years of laparoscopic cholecystectomy.

The disadvantage with the low-angled approach of the 'French' technique is that the instruments are quite often in contact with the intestine. The longer distance that has to be traversed in the peritoneal cavity by the instruments adds to the risk of inadvertent bowel damage. The duodenal thermal injury illustrates the higher risk of bowel damage when the insulation of the instrument is defective. The widely spaced mid-abdominal placement of the ports also limits its use after previous surgery (including lower abdominal surgery) and in pregnant women. The position of the port in relation to the surgeon makes 'palm grips' for the instruments more ergonomical as the target organ is forwards.

The 'American' technique employs a more cephalad approach to Calot's triangle. Access to the caudal surface of the triangle is limited. One grasper retracts the fundus of the gallbladder upwards, and it is important that the second grasper at Hartmann's pouch retracts laterally, not upwards, to pull the cystic duct perpendicular to the common bile duct. There is a tendency to pull Hartmann's pouch in the same direction as the fundus, which narrows the cystic duct–common bile duct angle, putting the common bile duct at risk of injury[17]. There is less contact between the instruments and the intestine, and the approach appears to be feasible more often in previously operated and pregnant patients. 'Pistol grips' are more ergonomical for the operator because the target organ is downwards.

Although the principles of cholecystectomy are similar in the 'French' and 'American' techniques, there are fundamental differences in the positions of the surgeon and the ports, and thus the access to Calot's triangle. In terms of postoperative pulmonary function, the 'French' method is better probably because of the lower placement of the ports. Whether the difference in pulmonary function translates into a clinical difference in chest complications can only be ascertained with a larger series.

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British Journal of Surgery 1996, 83, 942–945

Prospective study of microscopic lymph node involvement of the hepatic pedicle during curative hepatectomy for colorectal metastases

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Extensive lymph node dissection of the hepatic pedicle was undertaken in 100 consecutive patients undergoing curative hepatectomy for colorectal liver metastases in whom lymph node involvement of the hepatic pedicle was not macroscopically detectable. Microscopic lymph node involvement was found in 14 patients, in very different lymph node sites, and was related only to the number of metastases, extent of liver involvement and carcinoembryonic antigen level (all $P < 0{\cdot}05$).

Colorectal tumours that spread to the lymph nodes of the hepatic pedicle or coeliac region are generally considered to be metastases derived from metastases, that is lymphatic 'remetastasis' from liver metastases[1,2]. The incidence of macroscopic involvement of these lymph nodes varies from 1 to 10 per cent in major series of liver resection for colorectal metastases[1,3–5]. Low 5-year survival rates have been reported in these patients, despite complete resection of the macroscopically involved lymph nodes: one of the 24 patients (among 859 studied) in the series of Hughes *et al.*[6], for whom the discovery of such metastases was then considered a contraindication to hepatectomy, and 12 of the 100 patients (among 1818 in the series) in the study by the French Surgical Association[4], for whom the discovery of comparable metastases was not an absolute contraindication to hepatectomy.

However, microscopic involvement of pedicular and coeliac lymph nodes has never been extensively studied. Only three recent reports, using different methodological approaches, have examined the incidence of such microscopic spread during hepatectomy for colorectal liver metastases. Rosen *et al.*[7] performed systematic extrahepatic lymph node biopsy in 40 selected patients, among 280 who underwent curative hepatectomy, and found nine positive cases. Nakamura *et al.*[8] performed *en bloc* lymph node dissection of the hepatoduodenal ligament, retropancreatic and coeliac nodes in 22 patients, and discovered six positive cases. Schneebaum *et al.*[9], with radioimmunoguided surgery, found positive scintigraphic patterns in the portal area in 31 of 69 patients with resectable or irresectable metastases. These studies indicate that the data are inconsistent.

This article reports 100 consecutive cases of systematic wide lymph node dissection in patients who underwent curative hepatectomy for colorectal liver metastases, with no evidence of macroscopic lymph node involvement of the hepatic pedicle.

Patients and methods

One hundred consecutive patients who underwent curative liver resection for colorectal metastases were prospectively studied between October 1993 and December 1994. Seven institutions participated in the study. Inclusion criteria were: (1) complete resection of simple or multiple metastases, whatever their number, size or location; (2) no macroscopically detectable diseased lymph nodes (seen with the naked eye or by palpation) in the hepatoduodenal ligament, along the common hepatic artery, or in the coeliac region; and (3) examination of more than three lymph nodes per patient. The study was stopped when 100 eligible patients had been treated. During the study eight

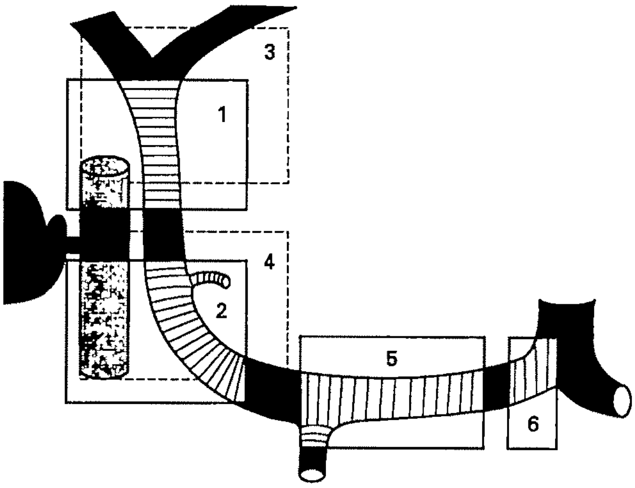

Fig. 1 Arbitrary division of lymph nodes into seven groups. An imaginary transverse line passing through the level where the cystic duct had been sectioned separates superior and inferior lymph node groups of the hepatic pedicle. Group 1, anterosuperior pedicular lymph nodes; group 2, anteroinferior pedicular lymph nodes; group 3, posterosuperior pedicular lymph nodes; group 4, posteroinferior pedicular lymph nodes; group 5, lymph nodes around the transverse part of the common hepatic artery; group 6, lymph nodes at the origin of the hepatic artery (coeliac); group 7, miscellaneous (mainly lymph nodes localized around a left hepatic artery inside the small omentum)

Paper accepted 13 October 1995

patients who exhibited macroscopic involvement of hepatic lymph nodes, confirmed by frozen section, were excluded; six further patients were also excluded because fewer than four lymph nodes were analysed.

Systematic wide lymph node clearance was performed, arbitrarily separating the lymph nodes into seven groups (*Fig. 1*): pedicular anterosuperior, pedicular anteroinferior, pedicular posterosuperior, pedicular posteroinferior, along and behind the transverse part of the hepatic artery, at the origin of the hepatic artery (coeliac), and miscellaneous (mainly along the left gastric artery and the inferior diaphragmatic group). The procedure began with cholecystectomy, and an imaginary line passing transversely, at the level where the cystic duct had been sectioned, permitted arbitrary separation of the superior and inferior lymph node groups of the hepatoduodenal ligament. Retropancreatic lymph nodes were allocated to the pedicular posteroinferior group.

Patient characteristics are shown in *Table 1*. Lymph node clearance was performed after hepatectomy in 77 patients and before hepatectomy in 23. Each lymph node was cut into 3-mm thick slices for histological examination.

Table 1 Clinical, biological and operative characteristics of the 100 patients

	Lymph node status		
	Negative ($n = 86$)	Positive ($n = 14$)	P
Age (years)			
Median (range)	62 (32–84)	57 (34–71)	0·090
Mean	60·4	55·4	
Sex ratio (M:F)	49:37	7:7	0·625
Dukes stage of primary tumour			
B	29	6	0·441
C	57	8	
Metachronous liver metastases			
Yes	40	6	0·799
No	46	8	
Resection of extrahepatic sites			
Yes	2	1	0·960
No	84	13	
CEA level (ng/ml)*			
Median (range)	26 (1–3070)	118 (3–7170)	0·02
Mean	130	668	
No. of liver metastases			
Median (range)	1 (1–6)	3 (1–8)	0·0002
Mean	1·8	3·4	
Extent of liver involved (%)†			
Median (range)	12·3 (5–60)	15 (10–60)	0·037
Mean	17·5	27·1	
Histological grade of liver tumour			
Well differentiated	56	7	0·400
Moderately differentiated	27	6	
Poorly differentiated	3	1	
Invasion of neighbouring organ by metastases			
Yes	7	3	0·555
No	79	11	
Maximum diameter of metastasis (cm)			
Median (range)	5 (1–17)	7 (3–22)	0·633
Mean	6·5	7·2	
Minimum tumour-free margin (mm)			
Median (range)	10 (0–35)	10 (2–30)	0·824
Mean	13·3	12·6	
Major hepatectomy‡			
Yes	51	12	0·037
No	35	2	

CEA, carcinoembryonic antigen. *Normal value < 7 ng/ml. †Assessed by intraoperative palpation. ‡Defined as resection of at least three segments according to Couinaud's classification

Table 2 Pathological characteristics of the 14 patients with positive hepatic lymph nodes

Patient no.	No. of nodes examined	No. of positive nodes	Sites of positive nodes*
1	11	4	Group 5 ($n = 2$), group 7† ($n = 2$)
2	4	2	Group 4, group 6
3	4	1	Group 4
4	9	1	Group 5
5	8	2	Group 4, group 5
6	8	1	Group 3
7	5	2	Group 4, group 5
8	5	2	Group 1, group 5
9	4	1	Group 5
10	16	1	Group 1
11	7	2	Group 4, group 5
12	14	2	Group 3, group 4
13	11	4	Group 1, group 2, group 3 ($n = 2$)
14	16	1	Group 1
Total	122	26	

*See *Fig. 1* for the designation of each lymph node group. †Inferior diaphragmatic lymph nodes

Statistical comparison between qualitative variables was performed with the χ^2 test, and between qualitative and quantitative variables with Student's t test.

Results

Fourteen of the 100 patients had microscopically involved lymph nodes according to final histological findings. Six of them had only one positive lymph node, six had two positive nodes and two four positive nodes. Details on the rate and locations of these involved lymph nodes are reported in *Table 2*. A total of 26 of the 122 lymph nodes (21 per cent) were positive. The four most frequently invaded groups of lymph nodes were, in decreasing order: the group along the transverse part of the common hepatic artery (group 5; seven of 26), the pedicular posteroinferior group 4 (five), the pedicular anterosuperior group 1 (five) and the pedicular posterosuperior group 3 (five).

Statistical correlation between microscopically positive lymph nodes and clinical, biological and operative characteristics of the patients is reported in *Table 1*. Positive nodes were not correlated with age, sex, Dukes stage of the primary tumour, histological grade of the liver tumours, their synchronous or metachronous appearance, associated resection of extrahepatic tumour sites, the invasion of a neighbouring organ, the maximum diameter of the metastasis, nor with free margins. Positive lymph nodes were significantly correlated with only three variables: the number of liver metastases ($P = 0{\cdot}0002$), raised blood carcinoembryonic antigen (CEA) level ($P = 0{\cdot}02$) and a high percentage of liver involvement ($P = 0{\cdot}037$). The extent of hepatectomy ($P = 0{\cdot}037$) reflected the number of metastases and/or liver involvement.

A total of 800 lymph nodes were resected. The percentages of nodes present in the different groups, their respective number and also their status (positive *versus* negative), are reported in *Table 3*. The group from the

Table 3 Details of anatomical and pathological findings relating to hepatic lymph node clearance in 100 patients

Node group (see *Fig. 1*)	Total no. of nodes*	No lymph nodes	Lymph nodes present	≥ 3 lymph nodes in group	Positive lymph nodes
Anterosuperior pedicular (group 1)	81	47	53	5	5
Anteroinferior pedicular (group 2)	78	51	49	7	2
Posterosuperior pedicular (group 3)	96	48	52	10	3
Posteroinferior pedicular (group 4)	197	16	84	30	4
Transverse hepatic artery (group 5)	220	3	97	31	6
Coeliac axis (group 6)	106	38	62	8	2
Miscellaneous (group 7)†	22	88	12	3	1
Total	800				

*Total number of nodes resected in the 100 patients; in group 1, 81 lymph nodes were removed from 53 patients. †Mainly lymph nodes along a left hepatic artery originating from the left gastric artery, also inferior diaphragmatic nodes

transverse part of the hepatic artery (group 5) and the pedicular posteroinferior (group 4) were those most frequently presenting lymph nodes. However, their invasion was not more frequent than that of the other groups.

No postoperative death occurred in this multi-institutional study. Morbidity occurred in 23 cases and was due to three types of complications. Seven patients had transient lymphatic leaks due to the lymph node clearance; in three of these it leaked through the abdominal wound. Six patients had a transient biliary fistula originating from the raw surface of the liver, for which percutaneous drainage was required. Five patients required drainage of pleural effusions and five suffered miscellaneous complications (pericarditis, peritonitis, septicaemia caused by infected catheters, transient liver failure, and ischaemic necrosis of a subsegment of the liver).

Discussion

This prospective study was performed because there have been no clear data concerning microscopic lymph node involvement in patients with colorectal liver metastases. Only a prospective approach, with systematic lymph node clearance and with systematic anatomical and pathological studies, could provide such information. It is now accepted that tumour cells in these lymph nodes are in fact metastases themselves originating from metastases[1,2]. Liver metastases originate from the haematogeneous dissemination of primary colorectal cells to the liver, growth in the liver, and then remetastasis to the lymph nodes via lymphatic drainage from the liver. In fact, lymph directed toward the portal pedicle represents only one part of the lymphatic drainage from the liver. Much of the lymph produced in the liver (0·35–0·6 ml per kg per min in the dog[10]) drains toward the portal pedicle, the coeliac region and then a node located between the aorta and inferior vena cava under the renal vein, before reaching the thoracic duct. Another, probably greater, component travels directly toward the posterior mediastinal chains through the ligaments that attach to the diaphragm[11]. Consequently, the study of infrahepatic lymph nodes is not an accurate reflection of total lymph flow from the liver.

In this prospective study, the rate of total pedicular nodal involvement was 19 per cent (22 of 114): eight and 14 patients with macroscopic and microscopic involvement respectively of 114 patients studied (100 included in the study, eight being excluded for macroscopic involvement and six for insufficient node sampling). The 14 per cent rate of microscopic lymph node involvement differs from the 27 per cent rate reported by Nakamura *et al.*[8]. However, nine of their patients did not undergo lymph node dissection (reason unspecified), and neither the sampling technique nor the number or sites of the lymph nodes was reported. In the series of Rose *et al.*[7], only a lymph node biopsy was performed and then only in selected cases.

Macroscopically involved lymph nodes of the hepatic pedicle or coeliac sites are well recognized poor prognostic factors, with a 5-year survival rate of 0–12 per cent[4,5,7]. However, no clear data have been reported concerning the therapeutic value of extensive lymph node clearance in these patients, possibly associated with concomitant radiochemotherapy in the pedicle and coeliac sites. A prospective multicentre study is needed to determine the value of these procedures.

The prognostic value of microscopic involvement of the hepatic lymph nodes is currently unknown. In the study of Rosen *et al.*[7], patients with apparently uninvolved nodes who were not submitted to biopsy did not fare as well as those with biopsy-demonstrated lack of involvement, which suggests that some patients with apparently normal lymph nodes had involvement that went undetected, as demonstrated by the present study. In contrast, Nakamura *et al.*[8] found no significant difference in survival between 16 patients with negative nodes and five with positive nodes. Also, it is surprising to find that, after curative hepatectomy for colorectal liver metastases, recurrence occurred so rarely in the hepatic pedicle and/or coeliac region, and yet 14 per cent of patients had microscopic involvement of the lymph nodes at the time of hepatectomy. Fortner[12] reported only 4 per cent of recurrences in the porta hepatis lymph nodes. Other series that examined recurrence after hepatectomy did not detail the site of extrahepatic intra-abdominal recurrence, but did not indicate a high percentage of recurrence in this region[7,13,14]. One reason for this omission could be that the regional recurrences were obscured by the occurrence of simultaneous distant metastases. However, as invaded lymph nodes are significantly related in the present study to a high number of liver metastases, to the degree of liver involvement and to a high CEA level, which are important poor prognostic factors, it is highly probable that microscopic lymph node involvement will be a poor prognostic factor. Whether it is a primary or a secondary prognostic factor remains to be elucidated.

It is noteworthy that 100 consecutive curative hepatectomies with lymphadenectomy were performed without mortality in seven different hospitals. Extensive lymphadenectomy is a tedious operative procedure, but did not cause any severe intraoperative difficulties. Lymphatic leaks were prolonged in 7 per cent of patients while other postoperative complications were directly related to the hepatectomy and not to the lymphadenectomy. This lymphadenectomy may have potentially long-term repercussions, due to changes that occur in vessels[15], and perhaps in the biliary tract, after their skeletonization. Angiography of the hepatic artery after such a procedure showed pathological changes in 42 per cent, consisting mainly of smooth and irregular stenoses, but occlusion in 8 per cent of cases[15].

The study of the rates of lymph nodes present in the different anatomical sites in the hepatic pedicle and coeliac region, and of the nodal sites affected, showed that there is no continuous chain progression from one lymph node to a neighbouring lymph node, but that 'skip' metastases are the rule. Consequently, no particular lymph node group can be considered to reflect nodal involvement, which means that limited sampling or a lymph node biopsy to estimate this lymph node involvement rapidly cannot be recommended.

In conclusion, extensive lymphadenectomy of the hepatic pedicle is routinely feasible without morbidity. In this study, a 14 per cent rate of lymph node involvement was found. The prognostic and therapeutic value of such lymphadenectomy is currently unknown and only a prospective randomized study comparing groups with and without lymphadenectomy will answer these questions.

Acknowledgements

The authors thank Ms Lorna Saint-Ange for editing the manuscript.

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British Journal of Surgery 1996, 83, 946–948

Elimination of fat emulsion particles from plasma during glucose infusion

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To determine the optimal rate of infusion of a fat emulsion (long-chain triglycerides; LCTs) for parenteral nutrition, the rate of elimination of triglycerides from plasma was measured on two occasions in three healthy subjects, once while receiving LCTs alone (study 1) and once while receiving a combined infusion of glucose and LCTs (study 2). In study 1 a hypertriglyceridaemic clamp was set up by raising the concentration of triglycerides to 2 mmol $\mathrm{l^{-1}}$ (60-min priming infusion at 0·2 g LCTs per kg body-weight per h) and maintaining this value for 300 min. In study 2 a constant infusion of glucose at a rate of 0·32 g per kg body-weight per h was given throughout the 420-min test, and the hypertriglyceridaemic clamp was set up after 70 min. The infusion of glucose induced a progressive increase in the mean(s.d.) concentration of insulin from 4·3(0·4) μU $\mathrm{ml^{-1}}$ to a plateau value of 11·0(0·2) μU $\mathrm{ml^{-1}}$ which was sustained during the last 310 min of the study. During the steady state of the hypertriglyceridaemic clamp, the concentration of triglycerides (2·16(0·17) *versus* 2·12(0·20) mmol $\mathrm{l^{-1}}$, $P = 0·26$), as well as the mean(s.d.) rates of infusion of LCTs (0·12(0·08) *versus* 0·12(0·04) per kg body-weight per h, $P = 0·38$), did not differ between studies 1 and 2. Thus, an infusion of glucose (and the associated physiological increase in the concentration of insulin) at doses commonly used in parenteral nutrition does not influence the rate of elimination of triglycerides from plasma in normal subjects.

The rate of elimination of triglyceride particles from plasma is regulated by several factors including haemodynamics, the activity of lipoprotein lipase[1], tissue microcirculation[2] and the capacity of high-density lipoprotein to donate apolipoproteins C-II, C-III and E to triglyceride particles[3,4]. The effect of increasing the concentration of insulin on the elimination of triglyceride particles from plasma remains to be determined, as fat emulsions are commonly infused together with glucose. The purpose of this study was to investigate the effects of a constant infusion of glucose on the rate of elimination of triglyceride particles from plasma.

Patients and methods

The subjects of the study were three healthy Japanese male research associates aged 32, 35 and 53 years.

Study 1

An emulsion of long-chain triglycerides (20 per cent LCTs; Intralipid; Otsuka Pharmaceutical, Tokyo, Japan) was infused after an overnight fast. A hypertriglyceridaemic clamp[5] was set up by raising the concentration of triglycerides in plasma to approximately 2 mmol $\mathrm{l^{-1}}$ using a priming infusion at a rate of 0·2 g triglyceride per kg body-weight per h and maintaining this concentration constant for 300 min. The total amount of triglycerides (g $\mathrm{h^{-1}}$) infused when the plasma concentration of triglycerides remained steady was divided by the body-weight of each subject, and the infusion rate was expressed as g per kg body-weight per h.

Study 2

A constant infusion of glucose at a rate of 0·32 g per kg body-weight per h was given throughout the 420-min test period. The infusion of LCTs was started when the blood glucose concentration had reached approximately 10 mmol $\mathrm{l^{-1}}$, and the plasma triglyceride level was clamped at nearly 2 mmol $\mathrm{l^{-1}}$ for 270 min. The rate of infusion of LCTs was calculated by the same method used in study 1.

Analytical methods

Concentrations of triglycerides in plasma were measured enzymatically at 10-min intervals with a New Cleantech TG System (Iatron Laboratories, Tokyo, Japan). Concentrations of glucose in plasma were determined by the glucose oxidase method with an APEC Glucose Analyzer (APEC, Danvers, Massachusetts, USA) at 10-min intervals. Concentrations of insulin in plasma were measured by radioimmunoassay (normal range after an overnight fast 3·4–11·8 μU $\mathrm{ml^{-1}}$). Concentrations of non-esterified fatty acids (NEFAs) were determined with the NEFA C-TEST WAKO (Wako Pure Chemical Industries, Osaka, Japan).

Statistical analysis

Data were expressed as mean(s.d.). The paired Wilcoxon test was used to compare rates of infusion of LCTs, levels of triglyceride and levels of NEFAs during the hypertriglyceridaemic clamp in studies 1 and 2.

Results

Study 1

The mean(s.d.) basal value of plasma triglyceride concentration was 0·80(0·05) mmol $\mathrm{l^{-1}}$. The concentration of triglycerides in plasma reached 2·09(0·93) mmol $\mathrm{l^{-1}}$ 60 min after the priming infusion. Thereafter, the concentration of triglycerides in the plasma remained steady at 2·16(0·17) mmol $\mathrm{l^{-1}}$ for 300 min with an infusion rate of 0·12(0·08) g triglycerides per kg body-weight per h. Concentrations of NEFAs in plasma were maintained

Paper accepted 27 October 1995

within a limited range (1·38(0·11) mEq l^{-1}) while plasma triglyceride concentration remained steady (*Fig. 1*).

Study 2

The mean(s.d.) basal plasma glucose concentration was 0·53(0·01) mmol l^{-1}. After commencing an infusion of glucose, the plasma glucose concentration reached a maximum value (11·8(0·4) mmol l^{-1}) after 150 min. Then the concentration began to decrease and reached a plateau at 8·2(1·3) mmol l^{-1} for the last 210 min of the study (*Fig. 2*). The mean(s.d.) basal concentration of insulin in plasma was 4·3(0·3) μU ml^{-1}. The plasma concentration of insulin reached a steady state at 11·0(0·2) μU ml^{-1} for a period of 310 min with the constant infusion of glucose (*Fig. 2*). Plasma triglyceride concentration remained steady at 2·12(0·20) mmol l^{-1} with a rate of triglyceride infusion of 0·12(0·04) g triglyceride per kg body-weight per h for 270 min, while plasma insulin concentration also remained steady. The basal mean(s.d.) plasma concentration of NEFAs fell from 0·98(0·12) to 0·38(0·05) mEq l^{-1} with the glucose infusion. When the infusion of LCTs was started, the level of NEFAs began to increase and then remained steady at 1·20(0·07) mEq l^{-1} (*Fig. 3*).

The rate of infusion of LCTs that stabilized the concentration of triglycerides in plasma did not differ between studies 1 and 2 ($P = 0·38$) (*Table 1*).

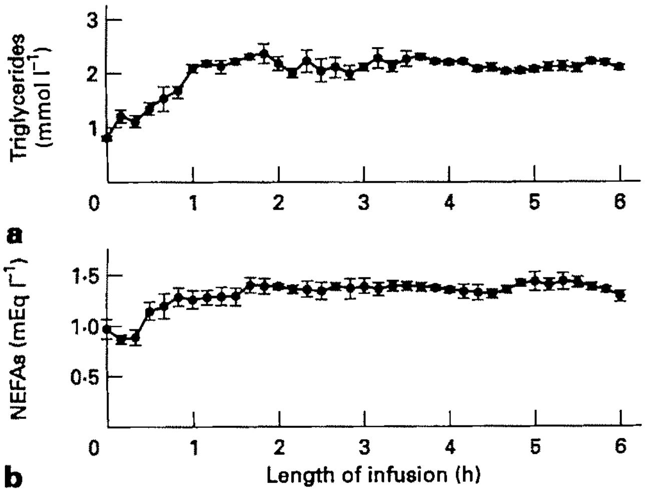

Fig. 1 Mean(s.d.) plasma concentration of **a** triglycerides and **b** non-esterified fatty acids (NEFAs). The concentration of triglycerides in plasma remained steady at 2·16(0·17) mmol l^{-1} with infusion of long-chain triglycerides at a rate of 0·12(0·08) g per kg body-weight per h (study 1)

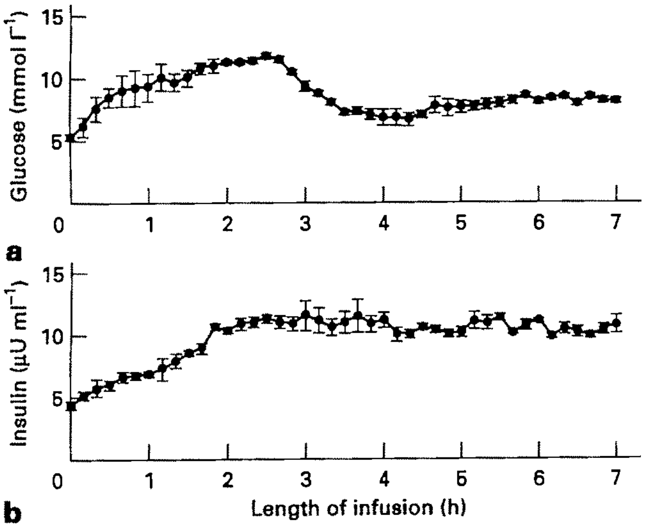

Fig. 2 Mean(s.d.) plasma concentration of **a** glucose and **b** insulin. The concentration of glucose in plasma continued to increase during the initial 150 min, and then remained stable at 8·2(1·3) mmol l^{-1} for the last 210 min. The concentration of insulin in plasma remained steady at 11·0(0·2) μU ml^{-1} over a period of 310 min (study 2)

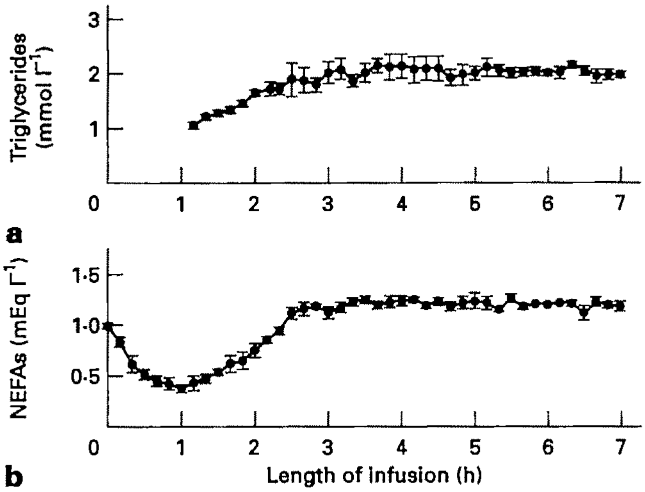

Fig. 3 Mean(s.d.) plasma concentration of **a** triglycerides and **b** non-esterified fatty acids (NEFAs). The infusion of glucose reduced the concentration of NEFAs in plasma. The concentration of triglycerides remained steady at 2·12(0·20) mmol l^{-1} with infusion of long-chain triglycerides at a rate of 0·12(0·04) g per kg body-weight per h during the period when the concentration of insulin remained steady. The concentration of NEFAs also remained steady at 1·20(0·07) mEq l^{-1} while the concentration of triglycerides was clamped (study 2)

Table 1 Infusion rates of long-chain triglycerides during the period when the plasma triglyceride concentration was stable

	Stable triglyceride concentration (mmol l^{-1})	Infusion rate of LCTs (g triglyceride per kg per h)
Study 1	2·16(0·17)	0·12(0·08)
Study 2	2·12(0·20)*	0·12(0·04)†

Values are mean(s.e.m.). LCTs, long-chain triglycerides. *$P = 0·26$, †$P = 0·38$ *versus* study 1 (paired Wilcoxon test)

Discussion

In patients receiving parenteral nutrition hydrolysis of fat particles in the bloodstream is essential for the degradation of triglycerides before further metabolism[6]. The activity of lipoprotein lipase on capillary endothelial cells plays a key role in the catalytic degradation of exogenous triglycerides[7]. Two types of lipase are involved in the hydrolysis of triglycerides. One is a hormone-sensitive lipase in adipocytes, which is inhibited by insulin. Thus, insulin inhibits the release of NEFAs from adipose tissue, with a subsequent reduction in the level of circulating NEFAs, as observed in the present study 2[8,9]. The other lipase is located on capillary endothelial cells. It is known as heparin-releasable lipase and is responsible for the hydrolysis of triglyceride-rich particles in the bloodstream. It has been reported that this lipase is activated by insulin[10–12]. However, the concentrations of insulin tested in studies of this lipase *in vivo* or *in vitro* seem unnaturally high (greater than $90\,\mu$U ml^{-1}) compared with concentrations of glucose commonly used in parenteral nutrition. In this study the effects of a constant infusion of glucose at a rate of 0·32 g per kg body-weight per h and the associated increase in the concentration of insulin within the physiological range (approximately $11\,\mu$U ml^{-1}) were compared with the rate of elimination of LCT particles from plasma.

In 1990 Carpentier *et al.*[5] described a hypertriglyceridaemic clamp technique for studies of lipid metabolism. The aim is to maintain the plasma concentration of triglycerides at a fixed level by controlling the rate of infusion of a triglyceride emulsion. Once the rate of infusion that maintains a constant plasma triglyceride concentration is known, it can be regarded as the rate of elimination of triglycerides from plasma. In the present investigation the infusion rate required to maintain a steady plasma triglyceride concentration did not differ between studies 1 and 2. Thus, a physiological increase in the concentration of insulin in response to an infusion of glucose, at doses commonly used in parenteral nutrition, did not affect the rate of elimination of emulsified triglycerides. These results support the findings of Thörne *et al.*[13], which suggested that administration of glucose and insulin as a euglycaemic hyperinsulinaemic clamp does not influence the rate of elimination of emulsified triglycerides. This study provides justification for the continuous infusion of a fat emulsion in combination with glucose, supporting the recommendation of MacFie *et al.*[14]. The rate of elimination of emulsified triglycerides from the plasma of Japanese subjects (0·12 g triglyceride per kg body-weight per h) was lower than that of Europeans, previously reported to be 0·15–0·20 g triglyceride per kg body-weight per h[6,14–16]. This difference might be due to a variation in lipoprotein lipase activity resulting from differences in dietary habits, namely the lower fat intake of the Japanese (25 per cent of total daily calories for the average Japanese adult).

Although the rates of elimination of fat emulsion particles from plasma were not different between studies 1 and 2, the level of NEFAs in study 2 was slightly lower than that in study 1. It is known that there is substrate competition for entry into cells. Under a condition of glucose shortage, available fuels enter cells in the following preference: (1) ketone bodies; (2) free fatty acids; and (3) glucose. By contrast, glucose is known to stimulate assimilation of free fatty acids[17]. This hypothesis was supported by the present study. The concentration of NEFAs in study 2 (1·20(0·07) mEq l^{-1}) was slightly lower than that in study 1 (1·38(0·11) mEq l^{-1}) (*P* not significant).

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British Journal of Surgery 1996, 83, 949–950

Short note

Morphological classification of abdominal aortic aneurysm in selection of patients for endovascular grafting

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The increasing frequency of up to 4 per cent of abdominal aortic aneurysm (AAA) over the past three decades[1] represents a major health problem. Since the first successful surgical graft replacement of AAA by Charles Dubost[2] in 1951, this conventional approach has proven to be the most appropriate method of preventing aneurysm rupture. The postoperative mortality rate has decreased significantly to less than 5 per cent in specialized medical centres[1]. Encountering older patients with severe concomitant morbidity, which may increase operative morbidity and raise mortality rates for aortic surgery, has led to an alternative form of AAA treatment: retrograde endoluminal transfemoral graft implantation, without laparotomy. This technique to exclude an AAA[3] was developed in the 1980s and the first clinical case was reported in 1991 by Parodi *et al.*[4]. This report is of a prospective clinical study focusing on investigation of the morphological structure of AAA. The purpose was to establish a dataset relating to the preoperative assessment necessary for the selection of conventional *versus* endovascular AAA reconstruction as the better method of repair.

Patients and methods

Prospective analysis was performed of standard aortography for evaluation of the visceral, renal and iliac arteries, and helical computed tomography (3-mm collimation in the region of the renal arteries, at 5-mm intervals thereafter) for precise measurement of the anatomical structure of the AAA. These tests formed a routine part of the preoperative assessment of 194 consecutive patients admitted for elective AAA repair in the period January 1993 to November 1995. Detailed measurements were compared with intraoperative findings. The study population consisted of 180 men and 14 women, ranging in age from 50 to 88 (mean 69) years, including 20 octogenarians. Surgical reconstruction was performed in all patients, with a tube graft in 69 and a bifurcated graft in 125.

Results and Discussion

On the basis of the data collected, a new procedure-related AAA classification system has been developed. Together with aortography, the profiles of the aorta in two-dimensional projection were used to identify clearly three distinct groups, based on the extent of aneurysmal disease (*Fig. 1*). Type I AAA was noted in 20 patients (10 per cent), type IIA in 53 (27 per cent), type IIb in 31 (16 per cent), type IIC in 63 (32 per cent) and type III in 27 (14 per cent). Regarding potential suitability for endovascular repair, a tube graft is appropriate only in type I; for types IIA, IIB and IIC a bifurcated graft is necessary. Type III is unsuitable for endovascular surgery at present due to the risk of occlusion of the renal arteries. Of the 194 patients, 104 (54 per cent) were good candidates for endovascular reconstruction, based exclusively on morphological criteria (types I, IIA and IIB). Apart from the above AAA classification system, there are several other criteria within types I, IIA and IIB that do not allow efficient and secure endovascular aneurysm repair with any of the present devices. Such criteria include iliac occlusive disease (23 of 104 patients), kinking or tortuosity (12 of 104) and a requirement for simultaneous revascularization of the renal (eight of 104) or inferior mesenteric (five of 104) artery or arteries. In the final analysis, only 56 (29 per cent) of the 194 patients would have been suitable for endovascular AAA repair.

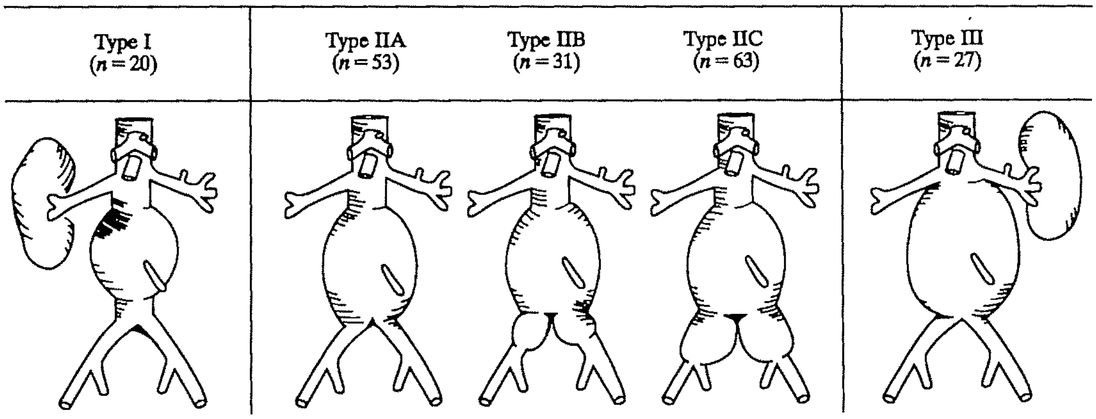

Fig. 1 Morphological classification of 194 abdominal aortic aneurysms

Paper accepted 6 February 1996

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British Journal of Surgery 1996, 83, 950

Short note

Compartment haematoma complicating closed fasciotomy

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Closed subcutaneous fasciotomy is an accepted method for decompression of a limb compartment when compartment syndrome is suspected or proven[1]. Fasciotomy of the anterior compartment through a limited skin incision is particularly appealing in patients undergoing lower limb revascularization because it releases the constricting fascia while avoiding extensive skin incisions which heal slowly and may translate into added morbidity[2]. Experience of a potentially grave complication associated with anterior fasciotomy following lower limb revascularization is reported.

Patients and methods

Over a 9-year period from 1981 to 1989 five men and eight women of age range 60–83 years developed an anterior compartment haematoma following closed (subcutaneous) fasciotomy of the anterior compartment in conjunction with lower limb revascularization. Fasciotomy was performed either immediately before or after the arterial surgical procedure; seven patients underwent thrombectomy or embolectomy and six had infrainguinal bypass. One patient received intra-arterial thrombolytic therapy before surgery and another underwent preoperative balloon angioplasty. All received intravenous heparin before or during the operative procedure. Three patients received postoperative heparin and two postoperative warfarin therapy. Clinical data were obtained from the patients' charts.

Results

The signs and symptoms of raised compartment pressure improved after closed fasciotomy in all patients, but reappeared when an anterior compartment haematoma developed. There was a mean lag period of 48 (range 6–96) h between fasciotomy and the diagnosis of anterior compartment haematoma. Nine patients required conversion to open fasciotomy to decompress the anterior compartment and evacuate the haematoma and four were managed conservatively with spontaneous resolution of the haematoma. Necrosis of the anterior compartment musculature occurred in one patient, resulting in permanent disability. Another patient underwent above-knee amputation after revascularization failed. Six patients required skin grafting to cover the open fasciotomy incision site, while five others healed by secondary intention. Hospital stay was prolonged in all patients.

Discussion

Despite its theoretical advantages, closed fasciotomy should be avoided in patients who require compartment decompression in the context of lower limb revascularization. The use of perioperative and intraoperative systemic anticoagulation sets the stage for the development of anterior compartment haematoma, which may in itself raise compartment pressure and cause ischaemic damage despite an open fascia. Furthermore, there is often a considerable delay in the recognition of this variant of a 'recurrent' compartment syndrome in a leg that is presumed to be decompressed. The risks of the closed procedure outweigh the theoretical advantages. Open fasciotomy should, therefore, be the procedure of choice for any suspicion of increased pressure in the anterior compartment following lower limb revascularization.

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Paper accepted 25 October 1995

British Journal of Surgery 1996, **83**, 951–952

Short note

Getting a grip: pinch *versus* scissors grip for small vascular anastomosis

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Imprecise following by the assistant may jeopardize small vascular anastomoses. Too much tension or failure to release the suture at the appropriate moment may tear out sutures, while too little tension may allow the anastomosis to bleed. When following a suture an assistant may use either the pinch or scissors grip (*Fig. 1*). These two techniques have been compared in a prospective randomized trial of 100 coronary artery bypass graft anastomoses.

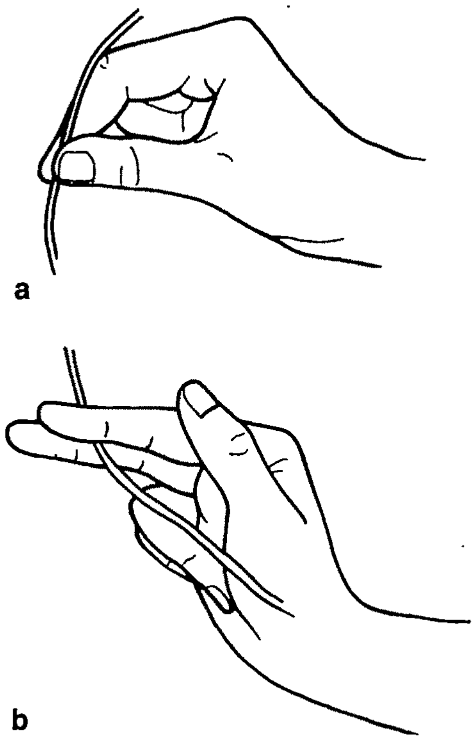

Fig. 1 **a** The pinch grip; **b** the scissors grip

Methods

One hundred coronary artery bypass graft ends were prospectively randomized for the assistant to use either the pinch or scissors grip. For each anastomosis both surgeon and assistant graded their satisfaction with the grip on a linear scale of 1 (poor) to 10 (excellent). All anastomoses were made with polypropylene: 5/0 for saphenous vein to aorta, 6/0 for saphenous vein to coronary artery and 7/0 for internal mammary artery to coronary artery.

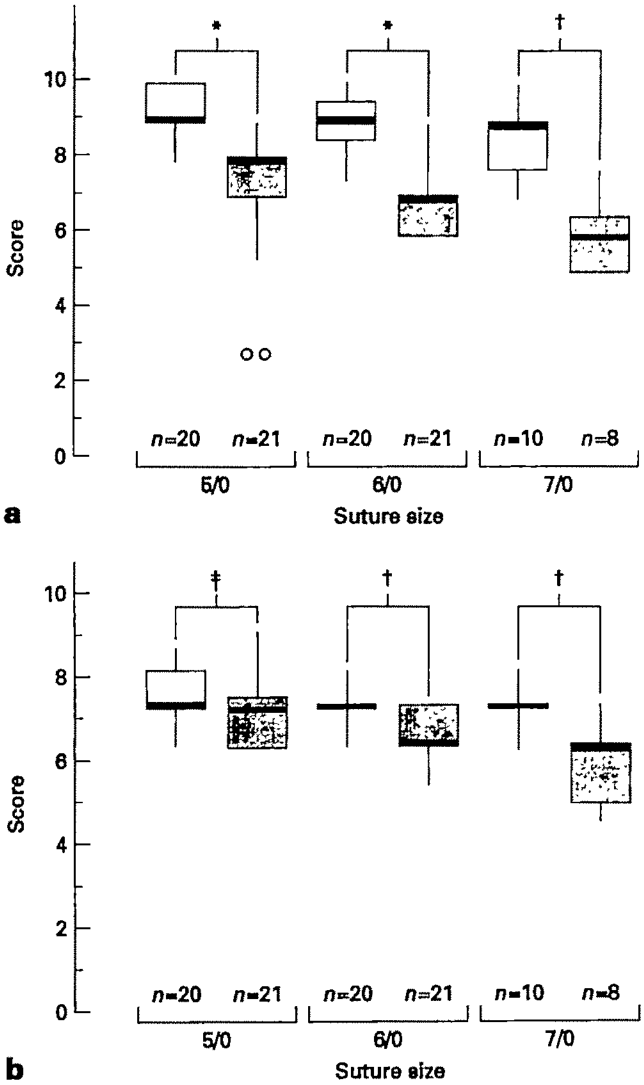

Fig. 2 **a** Assistant and **b** surgeon ratings of pinch (☐) and scissors (▨) grips by suture size. Horizontal bars represent the median, boxes the interquartile range; whiskers show the 10th to 90th centiles, and open circles are outliers. $^*P < 0{\cdot}0001$, $^\dagger P < 0{\cdot}0005$, $^\ddagger P$ not significant (Mann–Whitney U test)

Nine assistants, ranging from senior house officer to consultant, took part; four used the scissors grip routinely and five the pinch grip. The eight surgeons ranged from consultant to registrar.

Differences between grips were compared with the Mann–Whitney U test. $P < 0{\cdot}05$ was considered statistically significant.

Results

Assistants rated the pinch grip significantly better than the scissors grip for all size sutures (*Fig. 2a*). Surgeons did not notice a difference with 5/0 polypropylene but found the pinch grip superior for 6/0 and 7/0 (*Fig. 2b*).

Paper accepted 25 October 1995

Discussion

The pinch grip is better than the scissors grip during the creation of small vascular anastomoses. This superiority is likely to be due to the higher concentration of fine touch and discrimination receptors in the pulps of the fingers compared with the sides[1]. That surgeons did not notice a difference with 5/0 sutures suggests either that the benefits are less marked with larger gauge sutures or that surgeons are less critical. Assistants still rated the pinch grip superior with 5/0 polypropylene; they may be more alert to flaws in their following than surgeons. Given its superiority for small vascular anastomoses, the authors believe that the pinch grip should be used when following any suture.

Acknowledgements

The authors thank Messrs G. E. Venn, C. P. Young, J. B. O'Riordan and F. P. Shabbo, and their junior surgical colleagues for cooperation with the study.

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British Journal of Surgery 1996, 83, 953–956

Changes in the management of critical limb ischaemia

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A prospective study of all patients with critical limb ischaemia (CLI) who presented to a single vascular unit was undertaken for a 12-month period. There were 222 referrals in 188 patients, 80·2 per cent of which were emergency or urgent admissions. The majority (72·5 per cent) were initially investigated with colour duplex scanning to characterize the arterial lesion. Diagnostic angiography was performed in 35·1 per cent. An attempt at revascularization was made in 73·0 per cent of cases using percutaneous transluminal angioplasty (PTA) in 42·3 per cent, surgery in 24·3 per cent, and a combination of surgery and PTA in 6·3 per cent. Primary major amputation was required in 22 cases (9·9 per cent) and conservative treatments were used in 38 (17·1 per cent). The in-hospital mortality rate was 10 per cent with a limb salvage rate of 79 per cent. Diabetes was an independent risk factor for amputation (odds ratio 2·4, 95 per cent confidence interval 1·22–4·79, $P = 0{\cdot}012$). Median hospital stay was much shorter for patients treated by PTA (4·5 days) than surgery (16 days) or primary amputation (18 days). The complication rate of PTA requiring surgery was 5·5 per cent. CLI represents a large non-elective workload for a vascular unit. The increasing use of non-invasive duplex assessment and angioplasty plays a major part in the successful management of these patients.

Chronic critical limb ischaemia (CL1) endangers the leg or part of it. The European Consensus Document defines this as the presence of rest pain, ulceration or gangrene with maximum ankle or toe systolic pressures of 50 or 30 mmHg respectively[1]. In an ageing population this is now an increasingly common condition with an estimated incidence of 400–1000 per million population per year[2,3]. The outlook for these patients reflects the multifocal nature of atherosclerosis with a high mortality rate from cardiovascular disease (46 per cent at 5 years)[4] and a 25 per cent amputation rate at 1 year despite attempts at revascularization[5]. The optimal modern management of these high-risk patients demands a team approach combining the skills of non-invasive vascular imaging, interventional radiology and the vascular surgeon or physician. The aim of the present study was to evaluate the performance, in the authors' unit, of such a team involved in the management of CLI.

Patients and methods

For the purposes of this study CLI was defined as the presence of established rest pain, ulceration or gangrene with documented significant arterial disease on arteriography or colour duplex scanning. The Doppler pressure criteria of the European Consensus Document definition of CLI were not strictly adhered to as the authors have found these pressure thresholds to be of little prognostic value[6]. Acutely ischaemic limbs (symptoms for less than 2 weeks) and neuropathic diabetic foot lesions with palpable pulses and no lesion on duplex were excluded. In a small proportion of patients with extensive gangrene and/or a functionally useless limb, investigation with duplex or arteriography was considered to be inappropriate. Although the presence of arterial disease was not formally documented in these patients they were still included in the study.

Between January 1994 and December 1994 all admissions to the vascular unit for CLI were prospectively recorded on pro formas. The unit serves a catchment population of approximately 800 000 for vascular services. Coded unit audit data were not used as some referrals from medical and dermatological wards were never actually transferred to the vascular unit. The higher surgical trainees on the unit (K.V. and S.N.), through whom all referrals were made, collected the data prospectively. Demographic and clinical details together with the results of all vascular imaging and interventions were recorded. In-hospital outcome was recorded with particular emphasis on limb salvage, mortality and any procedural complications. Treatment was classified as reconstructive surgery, percutaneous transluminal angioplasty (PTA), primary major amputation (minor foot amputations excluded) or conservative therapies. The latter group included sympathectomy, analgesia, antibiotics, ulcer dressings and subsequent rehabilitation. Spinal cord stimulation and pharmacological therapy (i.e. iloprost) were not in routine use in the unit during this study. Patients who were confined to a wheelchair, had extensive necrosis or joint contractures which prevented walking were treated with primary major amputation. The methods used for PTA[7] and the selection of patients for distal bypass surgery[8] have been described elsewhere. All data were transferred on to a computerized database for analysis at the end of the study year.

Statistical analysis

Median and range were used for descriptive data. Comparisons of proportions were performed using the χ^2 test with Yates' correction. A multiple logistic regression analysis was performed with forward stepwise entry of variables to look for independent risk factors associated with amputation and death. This was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA).

Results

A total of 222 separate referrals were made for CLI in 188 patients (57 per cent men) during the 12 months of the study. A total of 198 limbs were entered into the study as ten of the 34 patients referred on more than one occasion had developed CLI in the other leg. Median age was 74 (range 31–94) years with the following atherosclerotic risk factors: smoking 80 (36·0 per cent), hypertension 75 (33·8 per cent) and diabetes 80 (36·0 per cent). Presentation was with rest pain in 78 (35·1 per

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Paper accepted 30 September 1995

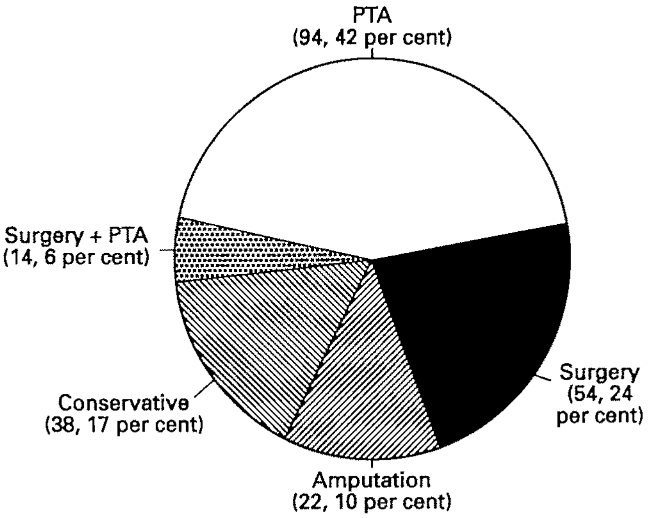

Fig. 1 Initial treatment strategy adopted in the 222 referrals with critical limb ischaemia during the study. PTA, percutaneous transluminal angioplasty

cent), ulceration in 89 (40·1 per cent) and gangrene in 55 (24·8 per cent). Eighty-nine cases (40·1 per cent) were emergency admissions, 89 (40·1 per cent) urgent admissions and 44 (20 per cent) planned elective admissions.

Non-invasive duplex scanning was the first line of investigation in 161 cases (72·5 per cent), digital subtraction angiography alone was used in 39 (17·6 per cent) and no diagnostic procedures were performed in 22 (9·9 per cent) although 11 of these had been investigated during a previous admission. Digital subtraction angiography was performed after an initial duplex scan in 39 cases. The treatment strategies adopted on the basis of these investigations are shown in *Fig. 1*. Eighty-five patients (78·7 per cent) referred for PTA were 'selected' on the basis of the initial colour duplex scan which was judged to show a lesion suitable for PTA. Angiography performed at the time of PTA confirmed the duplex findings in 86 per cent with minor discrepancies in the remaining cases. There were no major discrepancies that changed the planned approach to PTA. In a smaller number of cases the findings on the duplex scan were judged to be unsuitable for PTA and these patients were treated with surgery (20), primary amputation (two) and conservative therapies (15) based on duplex alone.

The overall in-hospital outcomes were: death in 19 patients (10 per cent) and limb salvage in 156 limbs (78·8 per cent). There were 144 patients (76·6 per cent) who left hospital alive with a viable (non-amputated) limb. Presentation with rest pain was associated with a better limb salvage rate ($n = 73$, 94 per cent) than ulceration and gangrene ($n = 106$, 73·6 per cent) ($\chi^2 = 11{\cdot}7$, 1 d.f., $P < 0{\cdot}001$). The multivariate analysis for risk factors associated with amputation included age, sex, smoking, hypertension, cerebrovascular disease, diabetes and ischaemic heart disease. Of these, diabetes was the only independent risk factor with an odds ratio of 2·4 (95 per cent confidence interval (c.i.) 1·22–4·79, $P = 0{\cdot}012$). The overall limb salvage rate in diabetics was 71 per cent compared with 86 per cent in non-diabetics. The significance of diabetes on limb salvage was lost, however, when the subgroup of patients undergoing revascularization with PTA or surgery was analysed (82 per cent diabetics *versus* 92 per cent non-diabetics; odds ratio 2·2, 95 per cent c.i. 0·75–6·5, $P = 0{\cdot}15$). There were no independent risk factors associated with death. The overall median hospital stay was 10 (range 1–97) days. A breakdown of hospital stay by procedure is shown in *Table 1*.

Surgery (n = *68*)

Thirty-three (49 per cent) of the surgical procedures performed for CLI were done on emergency lists (*Table 2*). There were three in-hospital deaths (4 per cent), seven failed procedures with subsequent amputation (90 per cent limb salvage) and seven major complications requiring further surgery. In 14 cases a combination of surgery and PTA was required: three preoperative inflow PTA procedures, one combined on-table PTA, five grafts after failed PTA and five grafts following PTA complicated by distal embolization.

Percutaneous transluminal angioplasty (n = *108)*

Seventy-two (66·7 per cent) of the PTA procedures were performed as urgent additions to elective sessions. The level of vessels dilated by PTA is summarized in *Table 3*. There were four in-hospital deaths (3·7 per cent), although none was directly attributable to the procedure. Technical success was achieved in 103 cases (95·4 per cent) resulting in limb salvage in 96 (88·9 per cent). There

Table 1 Median hospital stay for patients treated by surgery, percutaneous transluminal angioplasty or primary amputation

Treatment	Median (range) stay (days)
Surgery	16 (3–97)
Percutaneous transluminal angioplasty	4·5 (1–73)
Amputation	18 (7–91)

Table 2 Surgical procedures performed (68 operations). Some of these were combined segment reconstructions (aortobifemoral graft with a femoropopliteal bypass graft) so that the total number of procedures exceeds the number of operations

Surgical procedure	No.
Femorotibial bypass graft	28
Femoropopliteal bypass graft	21
Aortobifemoral graft	4
Femoral endarterectomy	4
Iliopopliteal bypass graft	5
Iliofemoral bypass graft	3
Thrombectomy	4
Extra-anatomic bypass graft	6

Table 3 Level of percutaneous transluminal angioplasty (PTA) performed in 108 attempted procedures

PTA level	No.
Suprainguinal	16
Infrainguinal	47
Infrapopliteal	16
Suprainguinal and infrainguinal	3
Infrainguinal and infrapopliteal	27

were nine groin haematomas (one requiring surgery), one groin infection and eight cases of distal embolization, five of which required surgery.

Major amputation (n = 42)

There were 22 below-knee and 20 above-knee amputations; three were bilateral. Twenty-two were primary amputations performed for extensive necrosis (six), functionally useless limb (four), unfit for reconstruction and PTA not possible (five), failed earlier graft (five) and unreconstructable despite operative exploration of vessels (two). The remaining amputations were performed following initial attempted PTA (12), surgery (seven) and conservative therapy (two). Four of the 22 primary amputees died (18 per cent mortality rate) in contrast to only one death in the remaining group (5 per cent mortality rate).

Conservative therapies (n = 38)

Eighteen cases in this group had undergone surgery or PTA in previous admissions limiting further options for revascularization. The other principal reason for adopting conservative measures was poor general health, reflected in the fact that eight (21 per cent mortality rate) died in hospital. Failure to control symptoms necessitating amputation occurred in two cases.

Discussion

The definition of CLI continues to be debated and the ankle pressure criteria the European Consensus Document for this clinically based study were not adhered to. The main concern that this raises is the inclusion of patients with rest pain and an ankle pressure greater than 50 mmHg where the limb might survive without revascularization[9]. Equally a number of truly threatened limbs would be excluded by such rigid adherence to an arbitrary threshold, which the authors have found to be of little clinical relevance[6]. Furthermore, Belcher[10] has demonstrated a gradual improvement in the outcome of CLI with increasing ankle pressure, but no discernible 'threshold' value that would predict inevitable amputation. This study therefore was based at a clinical level supported by duplex or angiographic demonstration of arterial disease in the vast majority of cases. This was a study of 'all comers' including all non-salvageable limbs with extensive gangrene, functionally useless limbs and patients with serious comorbid conditions preventing vascular intervention.

The management of CLI is a major part of the workload in any vascular unit. The 222 referrals in this 12-month study represent approximately one-quarter of all admissions to the authors' unit and are almost half the total inpatient workload, excluding elective admissions for PTA. This further highlights the emergency or urgent status of these referrals (80·2 per cent) with subsequent demands on interventional radiology and emergency surgery facilities. The use of colour duplex scanning to image the majority (72·5 per cent) with CLI has reduced the overall demand on angiographic facilities, leaving greater time for interventional procedures which can be planned using the 'map' provided by the duplex. Virtually all the duplex scans and PTA performed in this study were done during the working day with very little 'out-of-hours' requirement.

With continuing improvements in endovascular technology and expertise, an increasing proportion of patients with CLI can be treated by PTA. A deliberate policy in this unit to use PTA as first-line treatment whenever possible has resulted in a significant increase in the proportion of patients treated by angioplasty. In a previous retrospective study of CLI at the Leicester Royal Infirmary between 1988 and 1991, 23 per cent of patients were treated with PTA alone, in contrast with 42·3 per cent in the present study[11]. A similar, although less extreme, change in practice over the past decade is apparent from the two reported national surveys of CLI[3,5]. In the 1983 survey no patient was treated by PTA, 61 per cent had surgical reconstruction, 17 per cent a primary major amputation and 22 per cent medical treatment or sympathectomy. By 1993, 21 per cent were treated by PTA or thrombolysis, 42 per cent surgical reconstruction, 16 per cent primary amputation and 21 per cent minor or no treatment. The present study suggests that PTA can replace surgery as the primary therapy for CLI.

The advantages of PTA are well established for the high-risk, elderly, vascular patient. This study highlights the shorter hospital stay which reduces hospital costs. The initial results of PTA and surgery were comparable in this study, although follow-up data are required before the durability of these procedures can be known. Retrospective data on PTA for CLI in this unit have shown a 2-year patency rate of 78 per cent suggesting that PTA is a durable procedure[11]. PTA was associated with a complication rate (requiring surgery) of 5·5 per cent in this study. In a study by Belli *et al.*[12] a complication rate of 2·8 per cent requiring surgery for PTA in patients with rest pain was noted. Zeitler *et al.*[13] reported a similar value of 2·3 per cent for patients with Fontaine stage III and IV. This complication rate needs to be viewed in the context that PTA replaced surgery in many of these patients. Surgery was associated with a 4 per cent mortality rate (directly attributable to the procedure) and a 10 per cent rate of serious complications (bleeding, graft infection) which needed further surgery.

The in-hospital amputation rate in this study is almost identical to that of the recent national CLI survey (21 *versus* 21·5 per cent)[3]. The mortality rate in this study is lower (10 *versus* 13·5 per cent) but the significance of this is uncertain as most deaths in both studies came from symptomatic or no-treatment groups. Comparison with other studies of CLI is difficult as many quote only data from 1-year outcome. The initial primary major amputation rate in the Joint Vascular Research Group (JVRG) study was 19 per cent which increased to 26 per cent at the end of the first year[5]. The in-hospital amputation rate of 21 per cent in this study was therefore similar to the initial amputation rate of the JVRG study.

Diabetic patients had inferior limb salvage rates, partly due to the number referred 'late' with extensive gangrene and also the high incidence of distal disease not amenable to PTA or surgery. These patients often needed primary amputation. The outcome for diabetic patients suitable for either PTA or surgery was better, with a limb salvage rate of 82 per cent compared with 92 per cent for non-diabetics; a difference that did not reach statistical significance. These findings are in agreement with the results of previous studies examining the outcome of PTA and surgery in patients with CLI in whom diabetes was not a risk factor for a poor outcome[8,11].

This study has demonstrated the large non-elective workload associated with the management of CLI in a vascular unit. Non-invasive assessment of these patients with colour duplex scanning was performed in 72·5 per cent of cases, allowing efficient early selection of patients for PTA or surgery. An increasing proportion can be treated by PTA (42·3 per cent) rather than surgery (24·3 per cent), an important benefit for elderly, high-risk patients. The durability of these revascularization procedures requires further follow-up, but the initial in-hospital outcomes (10 per cent mortality rate, 78·8 per cent limb salvage rate) were similar to those in previous studies.

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British Journal of Surgery 1996, 83, 957–961

Effect of flow on the resistance of modelled femoral artery stenoses

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An accurate model of the pressure–flow relationship of a stenosis is necessary for the correct interpretation of haemodynamic measurements. Modelled femoral artery stenoses were tested *in vitro* and the pressure drop:flow ratio (resistance) was most accurately represented by a fixed component (R_f) combined with a variable component (R_v) that increased linearly with flow (Q) such that $R_v = S_v Q$. For stenoses of 68–94 per cent area, R_f increased from 3·2 to 77·7 milliperipheral resistance units (mPRU), while S_v increased from 0·009 to 0·578 mPRU ml^{-1} min and R_v was dominant for physiological flow rates. It was concluded that the approximation of a significant stenosis to a fixed resistance is incorrect.

The mean pressure gradient along a normal medium-sized artery (4–10 mm diameter) is small, even during periods of increased flow. Linear analysis has been used widely to predict the pressure–flow behaviour of normal arteries as, for laminar flow in a smooth tube, the pressure drop and flow rate are approximately linearly related[1]. In the adult human, the leg is supplied by the common femoral artery which has an internal diameter of approximately 7 mm. Occlusive disease of the femoral artery is a common cause of pain during exercise (intermittent claudication) and clinical experience shows that a partial occlusion of the common femoral artery only becomes symptomatic when it occupies more than 75 per cent of the area of the lumen[2]. May *et al.*[3] described such an occlusion as a critical stenosis.

A rigorous analysis of pulsatile blood flow through a network of partially occluded arteries presents a formidable fluid dynamics problem, so approximations to the true behaviour are required in order to apply the principles of haemodynamics to clinical practice. One approximation assumes that a stenosis can be represented simply by a tube with a smaller cross-sectional area than the normal vessel. In this case, assuming that the flow within the stenosis is laminar, the pressure drop ($\Delta P_{\mathrm{Poiseuille}}$) is related to the volume flow rate (Q) by Poiseuille's Law

$$\Delta P_{\mathrm{Poiseuille}} = \frac{8\mu L}{\pi r^4} Q \qquad [1]$$

where L is the length of the stenosis, r is the radius of the stenosis lumen and μ is the fluid viscosity. For a given flow geometry, equation [1] can be written:

$$\Delta P_{\mathrm{Poiseuille}} = \frac{k_1}{A_s^2} Q = R_P Q \qquad [2]$$

where A_s is the area of the stenosis and k_1 is a constant with dimensions of kg s^{-1}. The resistance of the stenosis R_P is given by the ratio of the pressure drop to the flow ($\Delta P/Q$) and equation [1] predicts that, for a given stenosis severity, the resistance is fixed and independent of the flow. This approximation of an arterial stenosis to a fixed resistance has been widely quoted to represent the pressure–flow relationship of diseased arteries[4–11]. In contrast, other authors have modelled flow through a stenosis using Bernoulli's equation[12,13]. The stenosis has a smaller area than the normal artery but, as the volume flow through the artery and the stenosis is the same, the velocity of the blood within the stenosis must increase. Thus, as the blood enters the stenosis its mass velocity and kinetic energy increase and the local pressure falls to conserve energy (Venturi effect). The reverse process occurs at the exit so that, if a non-viscous fluid were used, the net pressure drop across the stenosis would be zero. However, as blood is a viscous liquid, some of the kinetic energy is dissipated as heat and this is apparent as a net fall in pressure across the stenosis. In the modified Bernoulli approximation it is assumed that all the kinetic energy of the blood in the jet emerging from the stenosis exit is dissipated so that the pressure drop across the stenosis can be equated to the kinetic energy of the jet or:

$$\Delta P_{\mathrm{Bernoulli}} = \frac{1}{2} \rho v^2 = \frac{k_2}{A_s^2} Q^2 = S_B Q^2 \qquad [3]$$

where v is the velocity of the jet emerging from the stenosis and ρ is the density of the blood. Substituting into equation [3] yields:

$$\Delta P_{\mathrm{Bernoulli}} \approx 4v^2 \qquad [4]$$

where the pressure drop is expressed in mmHg (1 mmHg = 133 N m^{-2}), the density is given in g ml^{-1} (blood = 1·06 g ml^{-1}) and the velocity of the blood in the stenosis is given in m s^{-1}. This modified Bernoulli equation has been shown to be an accurate predictor of the pressure drop across a narrowed heart valve with the velocity of the emerging jet of blood measured by Doppler ultrasonography[14]. It is important to note that the relationship between the pressure drop and flow expressed by equations [1] and [3] represents extremes of the flow behaviour through a stenosis.

A further approximation was suggested by May *et al.*[15] who considered the overall pressure drop across a stenosis to be the sum of the entrance, body and exit effects. Expressing May's equation[15] in terms of the pressure drop (ΔP_{May}), volume flow rate (Q) and constants k_3 and k_4 (see Appendix) the following equation is obtained:

$$\Delta P_{\mathrm{May}} = \frac{k_3}{A_s^2} Q + \frac{k_4}{A_s^2} Q^2 = R_f Q + S_v Q^2 \qquad [5]$$

Paper accepted 5 September 1995

Equation [5] includes both a linear and a non-linear term representing the partition of energy loss between viscous and inertial processes. These fluid dynamic relations are only applicable if the fluid is incompressible and of constant viscosity, but for blood flow in arteries greater than 0·5 mm in diameter these conditions are likely to be valid[1]. The relationship between the pressure drop and flow predicted by equation [5] is dependent on the magnitude of the empirical constants k_3 and k_4. If the linear term is dominant then the stenosis may be represented as a fixed resistance (R_f) that is independent of the flow; if the non-linear term is dominant then the resistance is variable and will increase linearly with the flow ($R_v = S_v Q$). In order to determine the true behaviour of an idealized common femoral arterial stenosis, the pressure drop across a number of model stenoses was measured for constant flows over the normal range for the common femoral artery using a fluid with the same density and viscosity as blood. Relatively long, square-ended stenoses were used in order to model the situation where the Poiseuille resistance of the body of the stenosis would be measurable.

Materials and methods

A set of four 30-mm long, square-ended, cylindrical plugs of external diameter 6·7 mm were machined from an aluminium rod and a different diameter hole was drilled along the central axis of each to produce a set of axisymmetric area stenoses (*Table 1*). Each stenosis was used to connect two lengths of polyvinylchloride (PVC) tubing of internal diameter 6·7 mm, one leading from a computer-controlled constant flow pump and the other draining into a measuring container. The PVC tubes were made 1 m long to ensure that the flow was fully developed at the entrance of the stenosis. The side pressure upstream and downstream of the stenosis was measured by physiological pressure transducers communicating with the lumen by blunt-ended 1·5 × 40 mm needles. One transducer was placed 20 mm upstream of the stenosis entrance, the second transducer 200 mm downstream to allow flow disturbances created by the stenosis to stabilize. The transducers were connected directly to high-gain differential amplifiers incorporated in an analog/digital computer interface. The transducer outputs were sampled 100 times per second and averaged over 10 s to eliminate noise and random fluctuations in pressure. The transducers were zeroed and calibrated against a mercury manometer before each experiment and found to be reproducible to within 1 per cent.

A solution of glycerol in water (45 per cent) at 20°C was prepared with ρ and μ comparable to that of blood at body temperature ($\rho = 1060$ kg m^{-3}, $\mu = 0·0035$ N s m^{-2})[1]. The pump flow rate was varied to create a pressure drop across each stenosis in the range of 0–90 mmHg and accurately timed collections of the fluid were made once the pressure drop had stabilized. Q was calculated from the mass collected and the time of collection.

Steady flow in a cylindrical tube becomes turbulent at a critical flow rate above which the Reynolds number of flow exceeds a threshold value of around 2000. The Reynolds number (R_e) of the flow in the tube is related to the volume flow rate by:

$$R_e = \frac{4\rho}{\pi \mu d} Q \qquad [6]$$

where d is the internal diameter of the PVC tube. The mean flow in the common femoral artery of normal subjects varies between about 300 and 2000 ml min^{-1} when measured by Doppler ultrasonography[16]. In this study, a maximum flow of 2000 ml min^{-1} was used, resulting in a maximum Reynolds number of around 1900 in the PVC tube, i.e. the flow in the PVC tube was assumed to be laminar at all flow rates.

The pressure and flow measurements are expressed as mmHg and ml min^{-1} respectively in order to allow the resistances to be expressed as physiological peripheral resistance units (1 PRU = 1 mmHg ml^{-1} min, 1 PRU = 1000 mPRU). Poiseuille's Law predicts that, for the blood analogue used in this experiment, the resistance of a 1 m length of 6·7 mm diameter tube is 8·87 mPRU and the resistances of the stenoses predicted by equation [1] are shown in *Table 1*. The reproducibility of the pressure and flow measurements was found to be within a few per cent so only a small number of single pressure–flow measurements over a range of flows up to 2000 ml min^{-1} were required for subsequent analysis.

Table 1 Dimensions, severity and resistance of model stenoses predicted by Poiseuille's Law

Lumen diameter (mm)	Lumen area (mm^2)	Area stenosis (%)	Poiseuille resistance (mPRU)
1·6	2·0	94	81·6
2·3	4·2	88	19·1
3·0	7·1	80	6·6
3·8	11·3	68	2·6

Area of unoccluded 6·7 mm diameter tube = 35·3 mm^2. mPRU, milliperipheral resistance units

Results

There is a non-linear relationship between the pressure drop and flow for each stenosis (*Fig. 1*). The pressure–flow curve for each passes through the origin and, for a given flow, the pressure drop increases with stenosis severity. The same data are plotted as stenosis resistance ($\Delta P/Q$) against flow in *Fig. 2* and show a linear increase in stenosis resistance with flow. The resistance–flow relationship for each stenosis is represented by a positive flow-independent resistance (represented by the zero flow intercept on the resistance axis) and a flow-dependent resistance coefficient (represented by the slope of the resistance–flow line). The values of these components

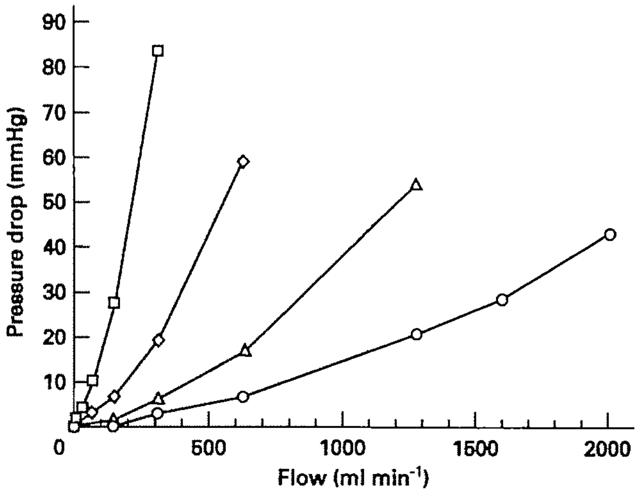

Fig. 1 Pressure drop across 30-mm long, square-ended, axisymmetric stenoses in a 6·7-mm diameter tube for steady flow of a blood analogue (45 per cent glycerol in water at 20°C). Stenosis severity is expressed as a percentage of the area of the unoccluded tube. (1 mmHg = 133 N m^{-2}.) □, 94 per cent; ◇, 88 per cent; △, 80 per cent; ○, 68 per cent

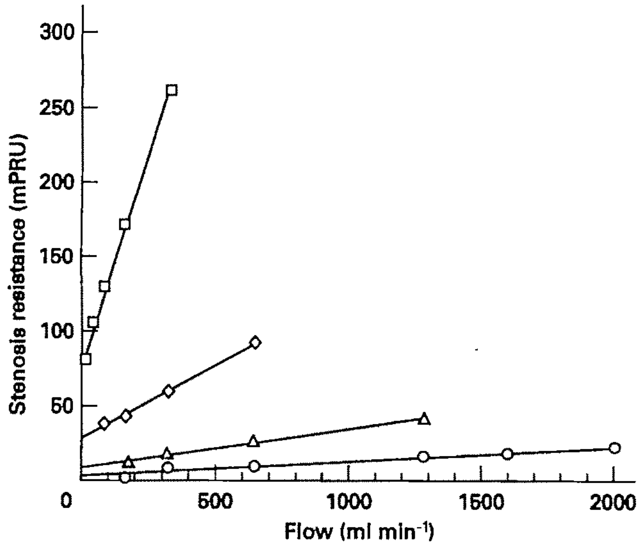

Fig. 2 Relationship between total resistance of 30-mm long, square-ended, axisymmetric stenoses in a 6·7-mm diameter tube and steady flow of blood analogue (45 per cent glycerol in water at 20°C). Stenosis severity is expressed as a percentage of the area of the unoccluded tube. □, 94 per cent; ◇, 88 per cent; △, 80 per cent; ○, 68 per cent

have been calculated using linear regression and are given in *Tables 2* and *3* together with their 95 per cent confidence intervals. *Table 2* shows that the flow-independent component of resistance (R_f) increases with stenosis severity and that the measured resistances are not statistically different from those predicted by Poiseuille's Law ($P > 0{\cdot}05$). *Table 3* shows that the flow-dependent coefficient of the stenosis resistance (S_v) is significant for each stenosis ($P < 0{\cdot}008$) and also increases with stenosis severity. *Fig. 3* shows that the relationship between S_v and stenosis severity is very non-linear, with a marked increase for a stenosis severity over 75 per cent. Using these results, the contribution made by each component of the stenosis resistance to the total pressure drop for each stenosis has been calculated for a flow of 350 ml min^{-1}, which is typical of the resting flow in the common femoral artery[16]. The results (*Table 4*) show that the flow-dependent component of the resistance is the greater for stenoses over 68 per cent.

Thus, the two-term non-linear equation [5] of the form proposed by May *et al.*[15] is the most accurate approximation of the haemodynamic effect of these model stenoses. The fixed or flow-independent resistance represents the effect of the body of a square-ended stenosis as the measured value is, within experimental error, the same as that predicted by Poiseuille's formula. However, the variable or flow-dependent resistance is significant for all stenoses and, for these modelled stenoses, dominates the flow-independent resistance for area stenoses over 68 per cent at flow rates greater than 350 ml min^{-1}.

Table 2 Measured flow-independent resistance of modelled stenoses compared with predicted Poiseuille resistance

Stenosis diameter (mm)	Area stenosis (%)	Flow-independent resistance (95 per cent confidence interval) (mPRU)	Predicted Poiseuille resistance (mPRU)
1·6	94	77·7 (64–92)	81·6
2·3	88	28·5 (19–37)	19·1
3·0	80	8·4 (0·9–16·0)	6·6
3·8	68	3·2 (−1·5–7·9)	2·9

mPRU, milliperipheral resistance units

Table 3 Measured flow-dependent resistance coefficient of modelled stenoses

Stenosis diameter (mm)	Area stenosis (%)	Flow-dependent resistance (95 per cent confidence interval) (mPRU ml^{-1} min)	*P*
1·6	94	0·578 (0·493–0·663)	0·0002
2·3	88	0·098 (0·075–0·122)	0·003
3·0	80	0·027 (0·016–0·037)	0·008
3·8	68	0·009 (0·005–0·013)	0·002

mPRU, milliperipheral resistance units

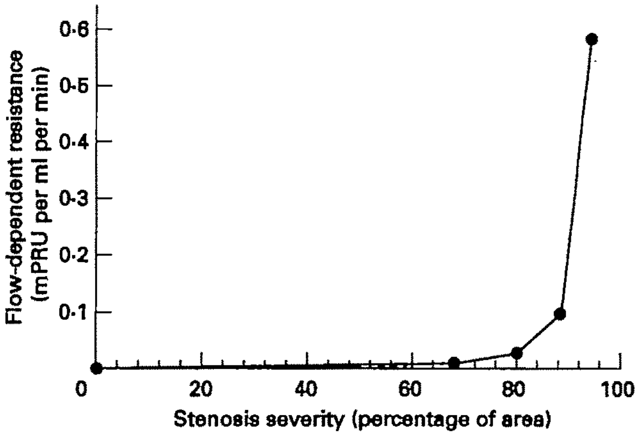

Fig. 3 Relationship between flow-dependent resistance coefficient and stenosis severity. Stenosis severity is expressed as a percentage of the area of the unoccluded tube. mPRU, milliperipheral resistance units

Table 4 Relative contribution of the flow-independent and flow-dependent components of modelled stenosis resistance at a flow of 350 ml min^{-1}

Area stenosis (%)	Flow-independent resistance effect (mmHg)	Flow-dependent resistance effect (mmHg)	Total pressure drop (mmHg)
94	27·2	70·9	98·1
88	10·0	12·1	22·1
80	2·9	3·2	6·2
68	1·1	1·1	2·3

1 mmHg = 133 N m^{-2}

Discussion

The objective measurement of the haemodynamic effect of occlusive arterial disease is an important tool in the management of patients with peripheral arterial disease. Haemodynamically significant residual disease proximal or distal to a bypass graft can lead to premature failure[17].

The most accurate assessment of proximal disease is by direct pressure measurement and is usually expressed as a pressure drop across the inflow segment at rest or during an artificially induced hyperaemia. The criteria used to plan an operative strategy are derived empirically by comparing preoperative haemodynamic measurements with the outcome in a population of patients. Similarly, the measurement of outflow resistance at operation has been shown to correlate well, but not perfectly, with outcome[9].

May *et al.*[15] suggested that the relationship between pressure drop across a stenosis and flow through it should be non-linear but presented no experimental evidence to support this hypothesis. Young and Tsai[18] predicted on theoretical grounds that the pressure drop across a stenosis can be modelled *in vitro* as a combination of linear and non-linear flow terms and showed experimentally that the empirical constants in the equation were related to the stenosis geometry. However, Young and Tsai considered only short, smooth stenoses and did not attempt to correlate the findings with clinical observations. Conventional measurements of arterial resistance are based on a single pressure drop and flow measurement and therefore cannot fully describe the non-linear haemodynamic behaviour of partially occluded arteries.

The test of any model is that it should be able to predict clinical observations. Using Doppler ultrasonography, Lewis *et al.*[16] found that the resting mean flow in the common femoral artery of both normal and symptomatic patients is around 350 ml min^{-1}. Schultz *et al.*[19] compared the pressure drop at different flow rates with the severity of arterial disease and found that normal iliac segments showed a pressure drop, at typical resting flows, of less than 4 mmHg. Thus, assuming that the haemodynamic effect of disease in arteries of this size is dominated by the flow-dependent resistance, the predicted severity of a critical stenosis of the common femoral artery can be estimated from:

$$\begin{aligned} \Delta P &\approx R_v . Q \\ &\approx S_v . Q^2 \\ 4 &\approx S_v . 350^2 \\ S_v &\approx 0{\cdot}033 \text{ mPRU ml}^{-1} \text{ min} \end{aligned}$$

which from *Table 3* would be produced by a single stenosis of about 80 per cent, a prediction that agrees closely with clinical experience[2].

Standard fluid mechanics theory states that entrance and exit effects cannot be accurately predicted from theoretical analysis and empirical measurements must be made to define the constants in the equations[20]. In addition, the independent non-linear relationship between stenosis severity and the coefficients of equation [5] means that even a small error in the measurement of the area of a near-critical stenosis will produce a large error in the estimated haemodynamic effect. This implies that the pressure drop across a stenosis can only be predicted accurately by using a two-term non-linear pressure–flow equation and that the constants in each term must be measured empirically for each stenosis. As there are two constants in the equation, pressure drop measurements must be made for, at least, two different flows.

In applying these results in practice it is important to take into account that arteries are not straight, rigid tubes and that the pressure and flow within them are not steady. However, a steady flow approximation can be used for continuous measurements provided that the mean values for a complete cycle, or the pressure at points of stationary flow (maximum and minimum), are employed. The results of this study also suggest why arterial impedance (the pulsatile equivalent of resistance) may not be a good predictor of outcome. The term impedance is, like resistance, borrowed from linear electrical circuit theory and, while it is a reasonable approximation to use for normal arteries, the fundamentally non-linear behaviour of a stenosis suggests that this approximation is invalid when significant arterial disease is present. This conclusion is supported by Law and Roberts[21] who observed that the outcome of an operation could only be accurately predicted when non-linear discriminant analysis was used to assess intraoperative impedance measurements.

The haemodynamic effect of an arterial stenosis is a combination of viscous (linear) and inertial (non-linear) losses. For a clinically significant stenosis in a vessel such as the femoral artery, the inertial losses predominate and the pressure drop across a short stenosis can be regarded as being proportional to the square of the volume flow. Stated another way, the pressure drop:flow ratio, or resistance, of a significant stenosis is not fixed but is dependent on the flow. The independent and highly non-linear relationships between stenosis severity and both the inertial and viscous losses is such that *in vivo* measurements of stenosis geometry alone would be an inaccurate measurement of the haemodynamic effect. Empirical measurement of the pressure–flow characteristics at more than one flow rate is required to quantify accurately the haemodynamic effect of an arterial stenosis. The authors conclude that, if parameters derived from both pressure and flow measurements are to be used as predictors of outcome, it is important that the more accurate non-linear equations are used to calculate such parameters if the maximum predictive potential is to be achieved.

Appendix

The equation derived by May *et al.*[15] is:

$$\Delta P_{\text{May}} = \frac{8\mu L}{r_a^2} v_a \left(\frac{A_a}{A_s}\right)^2 + \frac{4{\cdot}8\mu}{r_a} v_a \left(\frac{A_a}{A_s}\right)^{1{\cdot}5} + \rho v_a^2 \left(\frac{A_a}{A_s}\right)^2 \qquad [7]$$

where r_a is the radius of the unstenosed lumen, A_a is the area of the unstenosed artery, v_a is the velocity of the blood in the prestenotic artery, A_s is the area of the residual lumen of the stenosis and L is the length of the stenosis. Using the relationship:

$$Q = v_a A_a \qquad [8]$$

equation [7] can be rearranged to give:

$$\Delta P_{\text{May}} = \frac{\pi\mu(8L + 4{\cdot}8r_s)}{A_s^2} Q + \frac{\rho}{A_s^2} Q^2 \qquad [9]$$

where r_s is the radius of the stenosis. Equation [9] can be written as:

$$\Delta P_{\text{May}} = \frac{k_3}{A_s^2} Q + \frac{k_4}{A_s^2} Q^2 \qquad [10]$$

Acknowledgements

The authors thank Professor J. E. Field, F.R.S. of the Cavendish Laboratory, Cambridge, UK for permission to use his laboratory and workshop facilities for these experiments.

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British Journal of Surgery 1996, **83**, 962–963

Surgical workshop

Kidney retrieval from asystolic donors using an intra-aortic balloon catheter

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The retrieval of kidneys from asystolic or non-heart-beating donors has proved to be a valuable source of organs at a time when the shortage of donated kidneys continues to limit transplant activity[1]. The initial challenge in procuring such organs is to achieve rapid and effective cooling *in situ* as soon as possible after cardiopulmonary arrest. This manoeuvre limits the period of warm ischaemia with the intention of minimizing ischaemic damage[2]. Different techniques have been described including intraperitoneal cooling[3], extracorporeal cooling[4] and perfusion via an intra-aortic double-balloon triple-lumen catheter[5]. The latter is most widely used, and one potential problem is the inadvertent malplacement of the intra-aortic balloons. A simple modification of the established technique to facilitate accurate placement is described.

Paper accepted 1 November 1995

Surgical technique

The technique as described originally by Garcia-Rinaldi *et al.*[5] in 1975, involves insertion of the double-balloon triple-lumen catheter into the abdominal aorta via a femoral arteriotomy. Inflation of the caudal balloon at the aortic bifurcation and inflation of the cranial balloon isolates the segment of aorta from which the renal arteries originate (vertebral level L1). A plain abdominal radiograph can be taken to show the position of the catheter, which is radio-opaque. The authors' modification is to mix a small amount of Conray (May and Baker, Dagenham, UK) radiocontrast dye with the saline injected into the balloons to allow easier identification of the balloons on radiography. Using a mixture of Conray and saline in a ratio of 1:10 rather than neat Conray makes injection of the viscous liquid much easier.

Fig. 1 shows radiographs of a non-heart-beating donor's abdomen in which Conray has been used in the balloons. Initially the caudal balloon was retracted distal to the bifurcation and the cranial balloon was occluding the renal arteries and preventing perfusion. Once this situation was seen on radiography the balloons were deflated and repositioned, and repeat radiography confirmed the correct position of the balloons and catheter. Successful perfusion and retrieval of both kidneys resulted.

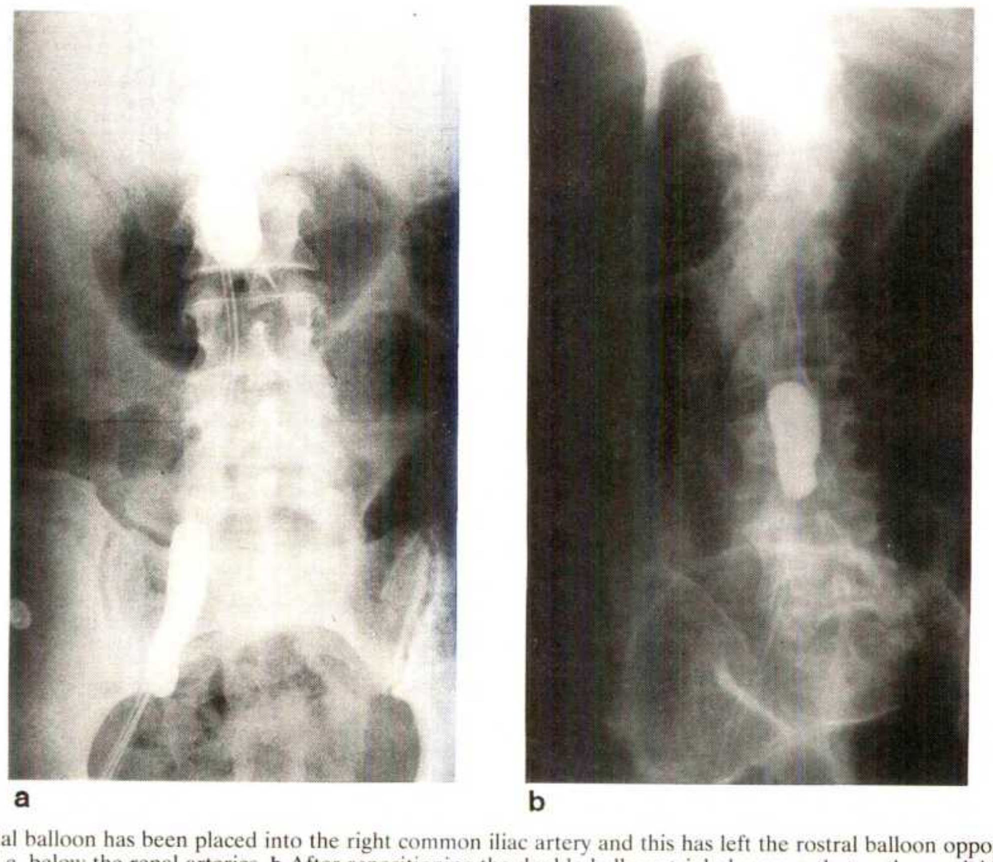
a b

Fig. 1 **a** The caudal balloon has been placed into the right common iliac artery and this has left the rostral balloon opposite the second lumbar vertebra, i.e. below the renal arteries. **b** After repositioning the double-balloon triple-lumen catheter, the caudal balloon is now jammed in the aortic bifurcation and the rostral balloon is at T12, i.e. above the renal arteries, which are now correctly isolated for *in situ* perfusion

Discussion

In Leicester the authors use a catheter supplied by Rusch (High Wycombe, UK) with a distance of 15 cm between balloons; this arrangement works well only when a caudal balloon sits correctly at the bifurcation. However, in an emergency situation with less than ideal X-ray facilities, it can be difficult to identify the catheter's position accurately. This simple modification allows easy visualization of the intra-aortic balloons and has improved the technical success rate of catheter placement.

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British Journal of Surgery 1996, 83, 964–968

Postoperative mortality in rectal cancer treated with or without preoperative radiotherapy: causes and risk factors

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Adjuvant preoperative radiotherapy in patients with rectal cancer improves local control and possibly overall survival. However, an increased postoperative mortality rate after radiotherapy has been observed in some trials. This study was based on 1399 patients in two randomized trials of radiotherapy. It reviewed the causes of death after operation and attempted to identify risk factors for postoperative mortality in patients with rectal cancer treated with or without high-dose (5 × 5 Gy) preoperative radiotherapy. The majority of deaths were from cardiovascular disease or infection. The risk of postoperative mortality was significantly increased in patients irradiated with a two-portal technique to a relatively large volume compared with those not given radiotherapy, but not in those irradiated with a four-portal technique to a limited volume. Age, sex, tumour stage and coexistent cardiovascular disease were independent risk factors for postoperative mortality. The risk of postoperative death in patients with rectal cancer is related to the preoperative radiotherapy technique.

Preoperative radiotherapy has been shown to improve local control[1–3] and possibly overall survival[4] in patients with primary rectal cancer.

In some randomized radiotherapy trials the postoperative mortality rate was significantly increased in patients with rectal cancer given irradiation compared with unirradiated controls[3,5]. In other trials the rates of postoperative death have been similar in irradiated and unirradiated patients[1,6]. Different radiotherapy trials have used different doses, target volumes, fractionations and portal techniques, and the potential risk of postoperative death associated with preoperative radiotherapy may thus depend on the radiation regimen and/or on other risk factors related to the individual patient. The increasing use of preoperative irradiation in patients with rectal cancer warrants further study of the possible adverse effects of this treatment.

This study was based on two randomized trials of preoperative radiotherapy in primary rectal cancer, both of which showed an increased mortality rate within 2 months after operation in patients given radiotherapy. The aim of this study was to review the causes of postoperative death, to analyse radiotherapy and different patient characteristics as risk factors for postoperative death, and to evaluate the interaction between radiotherapy and other risk factors.

Patients and methods

In 1980 the Stockholm Rectal Cancer Study Group initiated a randomized trial of preoperative short-term radiotherapy for operable rectal adenocarcinoma (Stockholm I Trial). Patients considered for curative surgery were randomized to radiotherapy followed by surgery or to surgery alone. Those allocated to preoperative radiotherapy received a dose of 25 Gy (5 × 5 Gy) by a two-portal technique to a relatively large volume[7]. By February 1987 the trial included 849 patients. An increased postoperative mortality rate was recorded in patients given radiotherapy compared with unirradiated patients (8 *versus* 2 per cent). The increased postoperative mortality rate was observed mainly in patients over 75 years of age. Details and results of the study were published previously[2,5,8].

Another Swedish radiotherapy trial compared preoperative with postoperative radiotherapy for primary rectal cancer. The preoperative irradiation dose was similar to that in the Stockholm I Trial, but the target volume was smaller and the field arrangements were different. No significant increase in postoperative mortality rate was reported[9]. In the light of these results the Stockholm Rectal Cancer Study Group initiated a new trial in March 1987 (Stockholm II Trial). The protocol was identical with that of the first trial, except that a four-portal technique was used, the target volume included only the lesser pelvis and patients aged 80 years or older were excluded. This second trial closed in May 1993, when 557 patients had been randomized. In the second trial the postoperative mortality rate was higher in patients given radiotherapy (2 per cent) compared with no irradiation (1 per cent), but this difference was not significant[4].

In all, 1406 patients were included in the two Stockholm trials. As five of the 849 patients in the first trial and two of the 557 in the second trial were not operated on, this study was based on 1399 patients who underwent surgery.

Study design

Sixty-nine of the 1399 patients died within 60 days of surgery. The cause of death in these patients was established from clinical records, autopsy reports and death certificates. The influence of age, sex, tumour stage and radiotherapy technique on the risk of postoperative death was analysed from data reported prospectively in all 1399 randomized patients in the two trials.

To assess other, putative, risk factors for postoperative death a nested case–control study within the cohort was performed. The cases were the 69 patients dying within 60 days of surgery and the controls were patients alive 60 days after operation. Two controls per case were selected at random from all patients in the two trials. As most postoperative deaths occurred in older patients the controls were matched for age (± 5 years) to permit analysis of risk factors strongly correlated with age. Similarly, matching for hospital was performed to achieve comparability in the availability of information.

A detailed retrospective review of clinical records in cases and controls was undertaken to obtain information about: preoperative morbidity, classified as cardiovascular, pulmonary, renal, gastrointestinal or other nature; preoperative physical status, assessed from the clinical notes on a scale of 1–4, based on the American Society of Anesthesiologists (ASA) score[10] (1, no symptoms of disease; 2, mild symptoms of disease; 3, severe symptoms of disease; 4, incapacitating symptoms of disease); results of preoperative electrocardiography and chest

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Paper accepted 31 October 1995

radiography, as interpreted by physiologists and radiologists before surgery; and administration of thromboembolic and antibiotic prophylaxis, the amount of preoperative bleeding and postoperative complications.

Statistical analysis

Survival was analysed by actuarial methods and comparisons of survival distributions made with the log rank test. Relative risks in the study cohort were estimated with a logistic regression model; relative risks within the case–control study were estimated with a conditional logistic regression model.

Results

Fig. 1 shows the survival rate in the 1399 patients during the first year after surgery. Within the first month 51 patients died, 41 of 692 (5·9 per cent) given radiotherapy and ten of 707 (1·4 per cent) not given radiotherapy ($P < 0{\cdot}0001$). In the second month after surgery 13 of 651 irradiated patients died compared with five of 697 unirradiated ($P = 0{\cdot}07$). From the third month after operation, the death rates were similar between the two groups of patients.

Causes of death

Table 1 shows the cause of death, according to allocated preoperative treatment, in the 69 patients who died within 2 months of operation.

Cardiovascular death occurred in 26 patients (38 per cent), 23 given radiotherapy and three not. Ten patients died from acute myocardial infarction, in eight cases the diagnosis being verified at autopsy and in two based on clinical evidence. Eight patients died from congestive heart failure, the diagnosis being based on autopsy findings in five cases and on clinical evidence in three. Eight patients died from pulmonary embolism, which was verified at autopsy in all but one.

Thirty-two patients (46 per cent) died from infection or septic complications, 22 given radiotherapy and ten not. Pneumonia was the cause of death in 12 patients, with the diagnosis being verified at autopsy in seven and based on clinical evidence in five. Fourteen patients died from intra-abdominal infection with peritonitis and septicaemia. In six patients the cause of death was septicaemia of unknown origin. In two of these patients autopsy also revealed acute myocardial infarction. However, due to the clinical signs of septicaemia these patients were classified as having deaths from infection.

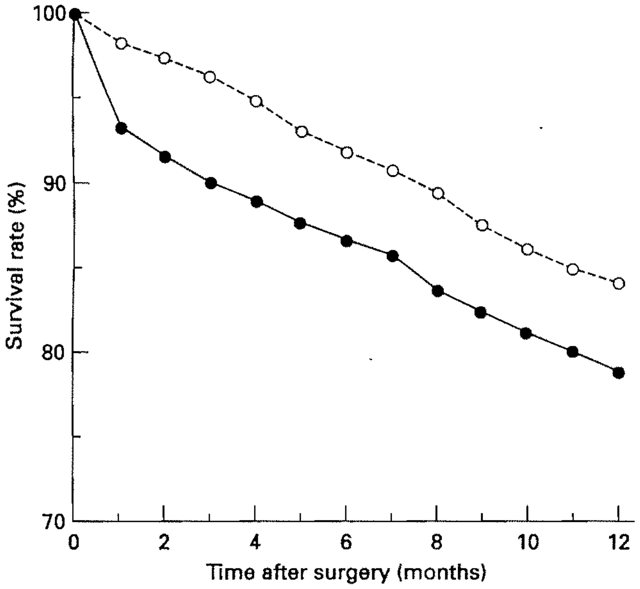

Fig. 1 Survival of 1399 patients for 1 year after surgery for rectal cancer with (———, $n = 692$) or without (– – –, $n = 707$) preoperative radiotherapy. $P = 0{\cdot}009$ (log rank test)

In the remaining 11 patients (16 per cent) the causes of death were uraemia in one, cerebrovascular bleeding in one, upper gastrointestinal bleeding in two and advanced cancer in seven.

In the first month after operation cardiovascular deaths occurred in 21 patients (41 per cent), death from infection

Table 1 Cause of death within 60 days of surgery for rectal cancer in 692 irradiated and 707 unirradiated patients

Cause of death	Radiotherapy	No radiotherapy	Total
Cardiovascular			
Myocardial infarction	9	1	10
Congestive heart failure	7	1	8
Pulmonary embolism	7	1	8
Total	23 (43)	3 (20)	26 (38)
Infection			
Pneumonia	9	3	12
Intra-abdominal infection	9	5	14
Septicaemia (unknown origin)	4	2	6
Total	22 (41)	10 (67)	32 (46)
Other	9 (17)	2 (13)	11 (16)
Total	54 (100)	15 (100)	69 (100)

Values in parentheses are percentages

Table 2 Distribution of age, sex, tumour stage and radiotherapy with corresponding relative risk of postoperative death within 60 days of surgery for rectal cancer (analyses based on 1399 patients)

	Death at ≤ 60 days ($n = 69$)	Alive at > 60 days ($n = 1330$)	Relative risk* (95% confidence interval)
Age (years)			
≤ 59	3 (4)	277 (21)	0·3 (0·1–1·0)
60–69	17 (25)	454 (34)	1·0
70–79	38 (55)	530 (40)	1·9 (1·0–3·4)
≥ 80	11 (16)	69 (5)	4·4 (1·8–10·4)
Sex			
M	50 (72)	783 (59)	1·0
F	19 (28)	547 (41)	0·5 (0·3–0·9)
Tumour stage			
Dukes A	18 (26)	395 (30)	1·0
Dukes B	17 (25)	406 (31)	1·0 (0·5–1·9)
Dukes C	13 (19)	389 (29)	0·8 (0·4–1·7)
Dukes 'D'	18 (26)	130 (10)	3·3 (1·6–6·8)
Unknown	3 (4)	10 (1)	
Treatment			
Surgery alone	15 (22)	692 (52)	1·0
Surgery and radiotherapy	54 (78)	638 (48)	3·4 (1·9–6·1)
Two-field technique	43 (62)	383 (29)	4·2 (2·3–7·8)
Four-field technique	11 (16)	255 (19)	1·8 (0·8–4·2)

*Adjusted for the other factors listed

in 24 (47 per cent) and death from other causes in six (12 per cent). In the second month after surgery the corresponding figures were cardiovascular five deaths, infection eight and miscellaneous five. The increase in the last group during the second month was mainly due to deaths classified as being from cancer.

Risk factors for postoperative mortality

The distribution of age, sex, tumour stage and radiotherapy technique in patients dying within 60 days of surgery and in those alive for this period is shown in *Table 2*. The relative risk of each factor was estimated with adjustment for the other factors. The risk of postoperative death was increased in elderly patients, in men and in patients with distant metastasis.

In the Stockholm I Trial (two-portal technique) the mortality rate within 2 months of operation was 10·2 per cent in irradiated and 2·6 per cent in unirradiated patients. In the Stockholm II Trial (four-portal technique) the corresponding figures were 4·1 and 1·4 per cent. Thus, the increased risk of postoperative mortality in patients given radiotherapy was attributable mainly to irradiation with a two-field technique; the increased risk in patients irradiated with a four-field technique was not significant.

The risk estimates for age, sex, tumour stage and radiotherapy for death within 30 days of surgery were similar to those calculated for mortality within 60 days (data not shown).

The frequency of other putative risk factors for postoperative death, recorded in the case–control study, are shown in *Table 3*. The crude relative risk values were estimated in a conditional logistic regression model. Factors that significantly increased the risk of postoperative death were analysed in a multivariate analysis. In this analysis the relative risk for each factor was adjusted for sex, radiotherapy and tumour stage as shown in *Table 4*. Coexisting morbidity significantly increased the risk of postoperative death. However, this was mainly due to an increased risk in patients with cardiovascular disease (relative risk 3·4). In patients with preoperative disease other than cardiovascular the risk of postoperative death was not significantly increased.

Table 3 Frequency of potential risk factors for postoperative death in patients dying within 60 days of surgery (cases) and in patients alive during the same period (controls)

	Cases (*n* = 69)	Controls (*n* = 138)
Preoperative morbidity*		
Cardiovascular	45 (65)	54 (39)
Other	20 (29)	32 (23)
None	21 (30)	62 (45)
Unknown	0 (0)	5 (4)
Performance status (ASA score)		
1	36 (52)	102 (74)
2	29 (42)	30 (22)
3 or 4	3 (4)	1 (1)
Unknown	1 (2)	5 (3)
Preoperative electrocardiogram		
Pathological	38 (55)	38 (28)
Normal	28 (41)	92 (67)
Unknown	3 (4)	8 (6)
Chest radiography		
Pathological	13 (19)	16 (12)
Normal	52 (75)	115 (83)
Unknown	4 (6)	7 (5)
Thromboembolic prophylaxis		
Yes	55 (80)	116 (84)
No	10 (14)	11 (8)
Unknown	4 (6)	11 (8)
Antibiotic prophylaxis		
Yes	61 (88)	123 (89)
No	3 (5)	4 (3)
Unknown	5 (7)	11 (8)

Values in parentheses are percentages. ASA, American Society of Anesthesiologists. *Groups were not mutually exclusive; some patients had both cardiovascular and other coexisting morbidity

Patients with evidence of ischaemic heart disease on preoperative electrocardiography were at increased risk of postoperative death (relative risk 4·6), but arrhythmia alone did not significantly influence mortality.

The risk of death was also significantly higher in patients with ASA score 2 or 3 than in those with ASA score 1.

The relative risk associated with a pathological chest radiograph was 1·9 (not significant). As most patients received thromboembolic and antibiotic prophylaxis the estimates for these factors were unreliable; the relative risks for patients who did not receive such prophylaxis were 2·5 and 1·8 respectively (not significant).

The median blood loss at operation was 750 ml. The risk of postoperative death was similar in patients with operative bleeding above and below this level (data not shown).

As mentioned above, the relative risk of postoperative mortality was significantly lower in women when analysed in the study cohort. The relative risk associated with sex was also analysed in the case–control study, and to estimate whether the increased risk in men was due to confounding from cardiovascular disease this was adjusted for. This analysis showed a non-significant lower relative risk in women (relative risk 0·8) and adjustment for cardiovascular disease did not change this estimate.

The risk of death within 30 days after surgery, related to the variables mentioned above, was also analysed. Risk estimates were similar to those for death within 60 days (data not shown).

The effect of interaction between preoperative radiotherapy and the presence of cardiovascular disease on the risk of postoperative death was tested in a logistic regression model with an interaction term. Within the

Table 4 Relative risk of postoperative death within 60 days of surgery for rectal cancer according to different risk factors

	No.*	Relative risk (95% confidence interval)†
Preoperative morbidity	198	2·9 (1·3–6·2)
Cardiovascular disease	198	3·4 (1·6–7·1)
Other	198	1·5 (0·7–3·2)
Pathological electrocardiogram	192	3·0 (1·5–6·3)
Ischaemic heart disease	192	4·6 (1·8–11·8)
Arrhythmia alone	192	1·9 (0·7–4·8)
Performance status (ASA score)		
1 *versus* 2 or 3	197	4·5 (2·0–10·5)

*No. of individuals with data available. †Matched analysis with conditional multiple logistic regression, adjusted for sex, radiotherapy and Dukes stage. ASA, American Society of Anesthesiologists context of this multiplicative model no evidence of interaction was found. Preoperative radiotherapy and cardiovascular disease are thus both independent risk factors. The highest relative risk of postoperative death is present in patients where both these factors coexist.

Discussion

Several randomized trials have shown that adjuvant preoperative radiotherapy reduces the local recurrence rate after surgery for rectal cancer[1,2,4,11]. However, an increased postoperative mortality rate in irradiated compared with unirradiated patients has also been observed in some trials. In two of these the increase was significant; in both trials radiotherapy was given through two opposed portals in large (5-Gy) fractions[2,3]. Other trials, without an increased postoperative mortality rate in patients given radiotherapy, have used either three- or four-portal techniques or another fractionation, usually over a period of 3–4 weeks[1,6,9,12]. In the present study, the postoperative mortality rate was higher in patients irradiated with a two-field technique to a large volume than in those irradiated with a four-field technique to a smaller volume, even after adjustment for confounding factors such as age, sex and tumour stage. Patients treated by the two-portal technique in the Stockholm I Trial were entered earlier than those treated by the four-portal technique in the Stockholm II Trial and it is possible that changes in management during this period were responsible for the lower mortality rate in the second trial. However, as the change in the control group was small this is unlikely. Thus, irradiation technique and irradiated volume are apparently factors in determining the risk of postoperative death associated with preoperative radiotherapy[13].

The causes of postoperative death in this study were mainly cardiovascular, thromboembolic or infection. Cardiovascular and thromboembolic complications have been increased after preoperative radiotherapy in other trials[3,14]. Radiation can induce vascular damage[15] and causes diminished plasminogen activator activity in endothelial cells[16]. It may be that preoperative irradiation affects the vascular endothelium resulting in coagulation disturbances with an increased risk of thromboembolic complications. The mechanism of such an effect, if present, is however unknown and warrants further study.

An increased risk of infectious complications, mainly wound infection, has also been reported after preoperative radiotherapy for rectal cancer[2,6]. Bacterial translocation occurs in patients with colorectal carcinoma and is more frequent in metastatic than in non-metastatic lymph nodes[17,18]. It may be that irradiation to the bowel further enhances bacterial translocation with subsequent postoperative infection. Radiotherapy has also been shown to depress the immune system through an effect on lymphocytes, which may influence the risk of postoperative infection[19].

The main risk factors for postoperative death were age, sex, tumour stage, radiotherapy and cardiovascular disease. Previous studies of postoperative mortality in patients with colorectal cancer have also reported that age, tumour stage and preoperative morbidity are important factors affecting operative mortality[20,21].

In this study and in that reported by Goldberg *et al.*[3], both showing an increased mortality rate after radiotherapy, the patients' median age was higher than that in the European Organization for Research and Treatment of Cancer trial, which reported a similar postoperative mortality rate in both groups. In comparison with the first Stockholm trial, the exclusion of elderly patients in the second Stockholm trial may have contributed to the reduction of postoperative mortality rate in irradiated patients. However, concomitant morbidity such as cardiovascular disease increases with age and it is likely that age is merely an indicator of other risk factors.

The relative risk of postoperative death in men was higher than in women, both when estimated from all randomized patients and within the case–control study. Cardiovascular disease is more common in men than in women, but even after adjustment for cardiovascular disease in the case–control study the difference in relative risk remained. This observation is difficult to explain but other, unknown, confounding factors may contribute. This study found that the risk of postoperative death in patients with distant metastasis was significantly increased. The same finding was observed by Goldberg *et al.*[3], who reported that nearly half of all postoperative deaths occurred in those treated palliatively, who comprised only one-third of the total number of patients.

A history of coexisting cardiovascular disease, signs of ischaemic heart disease on preoperative electrocardiography and an ASA score of 2 or 3 increased the risk of postoperative death. This is not surprising and has been found in previous studies of patients with colorectal cancer[20,22]. However, the important issue is to what extent the combination of radiotherapy and cardiovascular disease increases the risk of postoperative mortality. As radiotherapy and cardiovascular disease are independent risk factors for postoperative death, the combination of these will increase the risk in comparison with the effect of any single risk factor. Other independent risk factors, such as distant metastasis, will probably further increase that risk.

In summary, preoperative radiotherapy in rectal cancer reduces the rate of local recurrence and possibly improves survival, but it may also increase the postoperative mortality rate. To reduce the rate of postoperative death in irradiated patients, radiotherapy should be given through three or four portals and to a limited volume. Patients with cardiovascular disease and/or disseminated cancer should be carefully evaluated and exclusion of radiotherapy should be considered, especially in elderly patients. Thromboembolic and antibiotic prophylaxis should be mandatory and careful postoperative management may pre-empt complications.

Acknowledgements

The authors thank the members of the Stockholm Rectal Cancer Study Group for supplying data regarding included patients and Toom Singnomklao for help with the collection of data. This work was supported by research grants from the Cancer Society in Stockholm, the Swedish Cancer Society and Jerzy och Eva Cederbaums Minervafond.

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British Journal of Surgery 1996, 83, 969–972

Prospective analysis of the distal margin of clearance in anterior resection for rectal carcinoma

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The distal resection margin measured *in situ* at operation, on the fresh specimen and on the fixed specimen was analysed prospectively in 55 consecutive patients undergoing anterior resection for carcinoma of the rectum. There was obvious contraction in length from the operative margin to the specimen margin and to the fixed margin. As measured by contraction coefficients, contraction was greater in more proximal tumours than in distal ones. Eight of 55 patients had microscopic intramural spread in the fixed distal margin and the maximum spread was 12 mm. Taking contraction of the fixed margin into account, the extrapolated microscopic spread in the operative margin ranged from 0 to 47 mm.

Distal intramural spread of rectal carcinoma beyond the gross tumour edge occurs in about 25 per cent of patients. In only about 10 per cent of cases[1,2] does the tumour spread beyond 10 mm and these patients are likely to die from metastatic disease. A wide distal resection margin would not alter their prognosis. These results have led to the advocation of a minimum adequate distal margin of 2 cm or even less in anterior resection for carcinoma of the rectum[1–3].

The length of the distal margin, however, depends on when it is measured[4]. Margins are known to retract on division of the rectum and to retract further on fixation in formalin. Thus, the length of the distal margin can differ when it is measured on the serosal surface during operation, on the mucosal surface on opening the specimen, and on the mucosal surface of the fixed specimen either pinned or not pinned to a cork-board. Unfortunately, most studies do not define under what conditions the length of the distal margin has been determined. It follows that results obtained from studies using fixed specimens may not be appropriate to guide resection at operation.

In this study the relationships of the measured lengths of the distal margins during operation, on the fresh specimen as well as on the unpinned fixed specimen, were investigated with a view to correlating the histopathological appearance of intramural spread of the disease, to determine the necessary safe margin for transection at operation.

Patients and methods

All patients undergoing anterior resection for carcinoma of the rectum with either curative or palliative intent were studied prospectively between March 1991 and February 1993.

All patients underwent rigid sigmoidoscopy and biopsy to confirm the diagnosis. Colonoscopy was performed if the tumour was not obstructing. Other preoperative investigations included liver ultrasonography and plain chest radiography. In palliative anterior resection an effort was made to achieve locoregional clearance of the disease.

If technically feasible a distal margin of more than 3 cm in the unstretched rectum was taken, as measured at the time of operation after full mobilization of the rectum and just before rectal transection. For low-lying tumours where a 3-cm margin was not feasible, the mesorectum was excised completely as advocated by Heald *et al.*[5,6] and the longest distal margin that could possibly be achieved was taken using the Roticulator (US Surgical, Norwalk, Connecticut, USA) and the double stapling technique[7,8]. A resection margin of more than 2 cm was aimed for in these patients.

Data were entered prospectively on to a standard pro forma. Three measurements of the distal margins were made: (1) operative margin (OM); (2) specimen margin (SM); (3) fixed margin (FM).

The OM was taken as the distance between the palpable distal edge of the gross tumour on the serosal surface and either the lower edge of the cross clamp or the upper edge of the Roticulator (in the cases of double stapling) with the tumour elevated but not unduly stretched just before rectal transection. The SM was taken as the measurement between the distal cut edge of the fresh specimen and the nearest gross distal edge of the tumour on the mucosal surface in a natural unstretched state. The FM was taken as the measurement between the cut edge of the specimen to the nearest macroscopic gross tumour edge on the mucosal surface in the unpinned specimen fixed in 10 per cent formalin for 36–48 h. Two longitudinal blocks at 1-cm intervals from the distal rectal margins were obtained from the fixed specimens from the macroscopic tumour edge to the cut edges of the specimens. Three serial sections were obtained and the distance of microscopic intramural spread of tumour in the longitudinal blocks was noted if present. If the tumour was more than 3 cm from the distal resection margin and could not be included in the same block, a second block was taken including both tumour and adjacent non-tumour mucosa for evaluation of intramural spread. The distal cut edges of the fixed specimens and the distal doughnuts from the circular stapler were also examined for microscopic disease. Patients with malignant cells in the specimen edges or doughnuts were reported as having involved margins.

The degree of differentiation, Dukes stage and Jass stage were recorded. The transverse and longitudinal diameters of tumours were measured with the specimens cut open longitudinally in the fresh state. Tumours were assumed to be cylindrical and tumour volume was calculated according to the formula $\pi r^2 h$, where r is half the transverse diameter and h is the longitudinal diameter of the tumour.

Results

There were 29 men and 26 women in the study, of age range 28–81 (mean(s.d.) 62·3(12·4)) years. Some 49 patients underwent 'curative' anterior resection and six

Paper accepted 31 October 1995

Table 1 Distal margins of clearance

	All patients (n = 55)	Group 1 (n = 36)	Group 2 (n = 19)
Operative margin (cm)	4·2(1·8) (1·0–11·5)	5·1(1·6) (3·5–11·5)	2·4(0·6) (1·0–3·0)
Specimen margin (cm)	2·9(1·3) (0·5–7·0)	3·5(1·3) (0·5–7·0)	1·9(0·6) (1·0–3·0)
Fixed margin (cm)	2·3(1·0) (0·4–5·0)	2·6(1·0) (0·5–5·0)	1·7(0·8) (0·4–3·5)

Values are mean(s.d.) (range)

Table 2 Contraction coefficient

	All patients (n = 55)	Group 1 (n = 36)	Group 2 (n = 19)
CC_a (SM/OM)	0·7(0·2)	0·7(0·2)	0·8(0·2)
CC_b (FM/SM)	0·8(0·3)	0·8(0·2)	0·9(0·3)
CC_{a+b} (FM/OM)	0·6(0·3)	0·5(0·2)	0·7(0·4)

Values are mean(s.d.). CC, contraction coefficient; SM, specimen margin; OM, operative margin; FM, fixed margin

Table 3 Extrapolated microscopic involvement in operative margin

	All patients (n = 55)	Group 1 (n = 36)	Group 2 (n = 19)
OM_E (mm)			
Range	0–47·0	0–47·0	0–11·8
90th percentile	4·0	1·5	8·0
95th percentile	14·2	27·5	11·8

OM_E, extrapolated microscopic involvement in operative margin.

had palliative resections because of multiple distant metastases. Seven patients (13 per cent) had Dukes A disease, 23(42 per cent) had Dukes B and 25(45 per cent) Dukes C.

Patients were divided into two groups: group 1 consisted of 36 patients with distal operative margins of more than 3 cm; group 2 comprised 19 whose operative distal margins were 3 cm or less because a wider margin could not be achieved. The distal resection margins for all patients are listed in *Table 1*.

Contraction coefficients

There was an obvious contraction in length from the OM to the SM and also from the SM to the FM. The difference in the margins (OM *versus* SM, SM *versus* FM) was significant ($P<0·001$, paired-samples t test). The degree of contraction may be expressed by three contraction coefficients: (1) $CC_a = SM/OM$; (2) $CC_b = FM/SM$; and (3) $CC_{a+b} = FM/OM$. Contraction coefficients for all patients are shown in *Table 2*. The overall contraction coefficient (CC_{a+b}) of patients in group 1 was significantly less than that of those in group 2 ($P = 0·01$, t test).

Tumour volume ranged from 2·4 to 169·6 (mean(s.d.) 47·9(40·8) cm^3. There was no correlation between tumour size and the contraction coefficient ($r = 0·151$ for CC_a, $r = -0·045$ for CC_b and $r = 0·055$ for CC_{a+b}).

Intramural spread

Forty-seven patients (85 per cent) had no distal intramural spread, five (9 per cent) had a spread of less than 10 mm and only three (5 per cent) had a spread of 10 mm or more. Of the three patients with extended intramural spread, one was in group 1 and two were in group 2. The patient in group 1 had a low-lying tumour and bulky mesorectal disease. At operation the palpable mesorectal nodal disease was mistaken for the edge of the main tumour, which was in fact lower down, giving a discrepancy in measurement (OM 4·7 cm, SM 1·0 cm). This patient also had microscopic involvement of the resection margin and Dukes C disease. The two patients with extended intramural spread in group 2 had either liver metastasis or Dukes C disease; neither had involvement of the distal resection margin even though it was less than 3 cm at operation. The greatest distal intramural spread in the whole series was 12 mm and the margin was not histologically involved by malignancy in this patient.

Margin involvement

The resection margin was involved with malignant cells in two patients. The one in group 1 has been described; the other patient was in group 2 and had an OM of 3 cm and SM of 3 cm. There was minimal distal intramural spread but there was infiltration of the dome of the bladder. The involved margin was thought to be a skip lesion. Because of the possibility of the discontinuous nature of intramural spread, there is a theoretical chance that more patients might have been found to have discontinuous spread if more extensive margins had been taken.

Extrapolated microscopic spread in the operative margin

It is difficult, if not impossible, to determine the microscopic intramural spread in the OM *in vivo* before rectal transection. However, an estimate may be made of spread in the OM from microscopic spread in the FM and the degree of contraction from the OM to the FM in individual cases. The extrapolated microscopic spread in the OM (OM_E = intramural spread $\div CC_{a+b}$) is defined as the intramural spread that is extrapolated to the OM given the microscopic intramural spread in the fixed specimen and assuming that contraction of the distal rectal margin is homogeneous along its length. The OM_E may not represent the actual microscopic spread into the OM, but the authors believe that this is the best that can be obtained from the available data. The results for OM_E are shown in *Table 3*. The distribution of OM_E is markedly skewed because most patients did not have intramural spread. The 95th percentile for the whole group is at 14·2 mm, 27·5 mm in group 1 and 11·8 mm in group 2. There were only two patients whose OM_E was more than 14·2 mm. One was the patient who had bulky mesorectal disease leading to an incorrect OM measurement (OM 4·7 cm, FM 1·0 cm, intramural spread 10 mm, OM_E 47 mm). Another specimen showed a large discrepancy between the serosal and mucosal margins (OM 4·0 cm, FM 0·5 cm, intramural spread 3 mm, OM_E 24 mm). The high value of OM_E in these two cases was not due to extensive intramural spread but to inaccuracy in judgement of the mucosal margin at operation. These two cases were not taken into account in the subsequent suggestion of minimum OM based on extrapolated microscopic spread in the OM.

Provided the serosal and mucosal tumour edges correspond with each other, a minimum operative distal margin of 2 cm, or in the case of a very low anterior resection 1·5 cm, should be adequate for histological tumour clearance in most patients. An exception is the occasional case where the whole tumour is not bulky enough to be palpable at operation and the resection margin might well be grossly involved.

Long-term results

At the time of analysis the median postoperative follow-up interval was 28·0 (range 0·2–49) months. All six patients undergoing palliative resection died from the disease at a median of 4·5 (range 0·7–8·3) months. Both of the patients who were operated on with curative intent but shown to have involved margins received adjuvant radiotherapy to the pelvis after operation. One died from peritonitis as a result of perforation from radiation enteritis without evidence of recurrent disease at 11·4 months; the other is alive and disease free at 41·2 months.

Of the remaining 47 patients who were operated on with curative intent and with clear distal margins, 40 are still alive and disease free and one died from an unrelated cause. Six patients developed recurrent disease: five had distant metastases and only one (OM 2·0 cm, SM 1·5 cm, FM 1·0 cm) had extensive local recurrence which was thought to be due to perforation of the rectum distal to the tumour at the time of operation. Of the six with recurrent disease, two died from distant metastases and four are still alive with disease.

The survival rate of the 47 patients was 95 per cent at 3 years (92 per cent in group 1, patients in group 2 were all censored; $P = 0{\cdot}35$, log rank test) and the disease-free rate was 84 per cent at 3 years (88 per cent in group 1, 70 per cent in group 2; $P = 0{\cdot}19$, log rank test).

Discussion

The possibility of microscopic intramural spread of cancer cells in macroscopically normal-looking mucosa distal to the tumour in carcinoma of the rectum has been well recognized for decades – hence the 5-cm rule for distal clearance during anterior resection[9–11]. However, many surgeons have noticed that distal intramural spread is an unusual event and that when it occurs the prognosis of the patient does not usually depend on local clearance[1]. Moreover there is no relationship between the distal clearance margin and subsequent local recurrence and survival[12,13], so a 2-cm distal margin was well accepted[13,14]. However, the value of results obtained from fixed specimens remains questionable. In fact, Heald *et al.*[5,6] and others[15] advocated that the anus could be preserved provided it was not palpably invaded by tumour and a clamp could be placed across the bowel distal to the tumour. This policy resulted in margins ranging from 2 to 35 (mean 14) mm after fixation plus the stapler doughnut[16]. The present data indicate that judging the distance of the site of the tumour edge by palpation of the serosal surface at operation can be erroneous, and the discrepancy between the OM and the fresh SM can be as much as 3 cm or more. Therefore the surgeon may need to be guided by intraoperative sigmoidoscopy when Heald's approach is adopted.

Some authors have suggested that there is little shrinkage between the fresh and fixed specimens if the specimen is stretched and pinned out on a cork-board. This method was not used in this study and may account for the significant shrinkage from the SM to the FM.

Differences in the contraction coefficient for the two groups of patients may be explained either by different forces of stretch applied on to the rectum in the two settings or by a differential contraction for different parts of the distal rectum. As it is likely that more forceful stretch is applied to the rectum in the case of a very low difficult anterior resection than with a high tumour, the contraction coefficient for low resections should have been higher, but this was not supported by the data which suggested the reverse to be true, and it is likely that the distal rectum contracts less than the proximal rectum.

Local recurrence may result from a multitude of factors including involved distal margin, failure of clearance in the lateral margin, inadequate mesorectal excision or anastomotic implantation[14,15,17]. Judging the adequacy of the distal margin from the local recurrence may be inaccurate, and in this study distal microscopic spread was used as a parameter to determine the minimum OM of clearance. Intramural spread of tumour may or may not be contiguous[1]. Maximum spread can extend[1,2] from 34 to 50 mm, but when spread is more than 15 mm the patient is likely to die from metastatic disease. Thus it is suggested that a minimum operative resection margin of 2 cm for anterior resection or 1·5 cm for very low anterior resection is obligatory. Because there is a difference in contraction of the distal end in low tumours compared with the distal margin in high tumours, this is relevant in the context of very low anterior resection because a shorter minimum distal safety margin for low resection may enable sphincter-sparing operations to be conducted more frequently.

The three patients with extended intramural spread of more than 10 mm all had advanced disease, either Dukes C or distant metastasis. However, one of these patients had a microscopically involved margin resulting from an error in judging the level of the distal tumour edge at operation before transection. This patient had a distal resection margin of only 1 cm on the fresh specimen. The involved margin might have been avoided if the tumour had been palpated carefully at operation and intraoperative sigmoidoscopy performed so that the actual tumour edge could have been identified.

The other patient with an involved margin had a 3-cm length of distal margin. The tumour was poorly differentiated and there was also urinary bladder involvement. The involved margin was thought to be due to a satellite microscopic lesion and a routine 2-cm margin would not have been sufficient to remove it. However, these patients frequently have poorly differentiated tumours or Dukes C disease, and usually die from metastatic disease, so a more extended resection margin would not have altered the prognosis.

It is concluded that distal microscopic intramural spread in carcinoma of the rectum is uncommon and usually occurs within 15 mm in the fixed specimen.

Therefore, if the mesorectum is adequately excised, even taking contraction of the specimen into account, a minimum distal resection margin at operation should be 2 cm for high and 1·5 cm for low rectal tumours. However, palpation of the gross distal margin may not be accurate and intraoperative sigmoidoscopy should be used in doubtful cases.

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British Journal of Surgery 1996, 83, 973–977

A randomized controlled study of the effect of bedside leucocyte depletion on the immunosuppressive effect of whole blood transfusion in patients undergoing elective colorectal surgery

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In a randomized study the effect of whole blood transfusion *versus* bedside leucocyte-depleted blood transfusion on lymphocyte proliferation, $CD4^+:CD8^+$ ratio, and levels of soluble interleukin 2 receptor (sIL-2R) and interleukin (IL) 6, as well as on the development of postoperative wound infection and intra-abdominal abscess, was assessed in 60 patients undergoing elective colorectal surgery. Transfusion with whole blood induced a significant decrease in lymphocyte proliferation and $CD4^+:CD8^+$ ratio ($P < 0{\cdot}01$) as well as a significant increase in sIL-2R and IL-6 levels ($P < 0{\cdot}01$). Furthermore, transfusion with whole blood was accompanied by a significant increase in postoperative infectious complications ($P < 0{\cdot}01$). In patients transfused with leucocyte-depleted blood only slight and transient changes were observed, which were not significantly different from those observed in non-transfused patients.

Allogeneic blood transfusion increases the incidence of postoperative bacterial infection in patients undergoing abdominal[1–5], cardiac[6] or orthopaedic[7] surgery, and may be a risk factor for the development of multiple organ failure after major abdominal surgery[8]. In the majority of published studies blood transfusion has been shown to be a significant prognostic marker for the development of postoperative infectious complications[1–3,9].

The association between allogeneic blood transfusion and postoperative infectious complications may be due to its immunosuppressive effects. Laboratory and clinical data have demonstrated impaired cell-mediated immunity following blood transfusion, particularly that mediated by T lymphocytes and natural killer (NK) cells[1,10–13]. In human studies allogeneic transfusion is followed by decreased numbers of $CD4^+$ helper/inducer cells[13–15] and increased $CD8^+$ suppressor/cytotoxic cells[14], resulting in a decreased $CD4^+:CD8^+$ ratio. The mechanism leading to transfusion-induced immunosuppression is not completely understood and few studies have attempted to correlate immunological changes with clinical outcome. Furthermore, it is not yet clearly documented which elements in allogeneic blood transfusion may mediate the immunosuppressive effects, although both cellular and humoral components may play a role[1,16,17].

It has previously been shown that leucocyte-depleted blood transfusion prevents the decrease in NK cell activity as well as the development of postoperative infectious complications compared with whole blood transfusion in patients undergoing elective colorectal surgery[1]. The aims of the present study were to investigate the effect of leucocyte depletion on postoperative changes in certain other immune parameters in a part of the same patient population.

Patients and methods

Sixty consecutive patients[1] admitted for elective colorectal surgery were studied. When blood transfusion was indicated and the patients had given informed consent they were randomly allocated by means of sealed envelopes to receive either whole blood or blood depleted of leucocytes. Leucocyte depletion was performed by passing whole blood through a filtering device (Pall-filter, RC 100; MEDA, Copenhagen, Denmark), thereby reducing the white cell count by 99·98 per cent. Red cells and plasma passed through the filter, which was mounted at the bedside and placed between the blood bag and the transfusion tube. The filter is designed for filtration of 1–2 units whole blood. All blood transfusion units used were kept in the blood bank at +4°C for less than 3 weeks.

The indications for blood transfusion were a preoperative haematocrit of less than 0·35. Intraoperative and postoperative transfusions were given according to the haemodynamic status of the patient.

Venous blood, for the analysis of lymphocyte proliferation to PHA (phytohaemagglutinin) stimulation and distribution of $CD4^+$ and $CD8^+$ cells, serum soluble interleukin (IL) 2 receptors (sIL-2Rs) and plasma IL-6, was obtained before skin incision and on the morning of days 3, 7 and 30 after operation.

Flow cytometric cell-surface marker analysis and lymphocyte proliferation assays were performed as described previously[18].

Measurement of sIL-2R and IL-6 levels was performed using commercially available enzyme-linked immunosorbent assay test kits (T-cell Science, Cambridge, Massachusetts, USA, and Immunotech SA, Marseille, France respectively)[19,20].

Data on sex, age, diagnosis, operative procedures, duration of surgery, blood transfusion during hospitalization and development of postoperative infectious complications were recorded. Abdominal wound infection was defined as accumulation of pus with spontaneous discharge or requiring surgical drainage. Patients with wounds with purulent discharge after return home were included in the group with infection. Deep surgical infection consisted of intra-abdominal abscess, defined as an intraperitoneal or pelvic collection of pus diagnosed by ultrasonography, laparotomy or spontaneous discharge. Follow-up examination included daily inspection by an independent assessor from day 3 after operation until suture removal or patient discharge. All patients were followed in the outpatient clinic for 30 days after operation. Standard antibiotic prophylaxis was given as a single peroperative intravenous dose of cefuroxime 3 g and metronidazole 1·5 g in all patients.

Data were recorded on standard forms for computer analysis. Differences between groups and variables of patients were tested with Fisher's exact test or the Mann–Whitney *U* test where appropriate. Differences within groups were analysed by means

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Paper accepted 31 October 1995

of the Wilcoxon rank sum test. $P < 0{\cdot}05$ was considered significant. Values are given as median (range).

The study protocol was approved by the local ethics committee.

Results

Thirty-four patients (57 per cent) received blood transfusion. Fifteen received leucocyte-depleted blood and 19 whole blood transfusion. Clinical and surgical data are shown in *Table 1*. There were more women in the transfused groups and the duration of surgery was longer in those receiving transfusion. However, there were no differences in any clinical or operative data between the two transfused groups. Seven of the 19 patients in the group transfused with whole blood developed nine infectious complications, compared with none in the other two groups (*Table 1*). Infection was diagnosed a median of 12 (range 8–28) days after surgery.

The amount of blood administered was similar in the two transfused groups (median 2 (range 1–3) units before, during or after operation in both groups). The distribution of patients receiving transfusion before, during or after operation was also similar in the two groups. Before operation five of 19 patients received whole blood transfusion and six of 15 received leucocyte-depleted blood. During and after operation the proportions were 12 of 19 *versus* six of 15 and 13 of 19 *versus* nine of 15 respectively. All transfusions given after operation were administered within 6 days of surgery. A total of 31 units blood was used in patients receiving leucocyte-depleted blood and 43 units in those receiving whole blood.

Lymphocyte proliferation was significantly decreased in the postoperative period in patients transfused with whole blood compared with that in the other two groups, where the level was almost unchanged throughout the whole period (*Fig. 1*). There was no significant difference at any time in the percentage of CD4$^+$ cells between any of the groups. However, the proportion of CD8$^+$ cells increased at days 3 and 7 in the group transfused with whole blood, and was respectively twofold and threefold higher ($P < 0{\cdot}01$) than in the other groups. This resulted in a significant decrease in the CD4$^+$: CD8$^+$ ratio (*Fig. 2*).

The serum level of sIL-2RF in the authors' laboratory[19] ranged from 155 to 480 (median 340) units/ml. There were no differences in the preoperative level of sIL-2R between the groups (*Fig. 3*). During the first week after surgery a transient and non-significant increase was observed in the non-transfused group as well as in patients transfused with leucocyte-depleted blood (*Fig. 3*). In contrast, the group transfused with whole blood exhibited a considerable increase in sIL-2R concentration during the first week after surgery ($P < 0{\cdot}01$), and even though it decreased thereafter the level was still signifi-

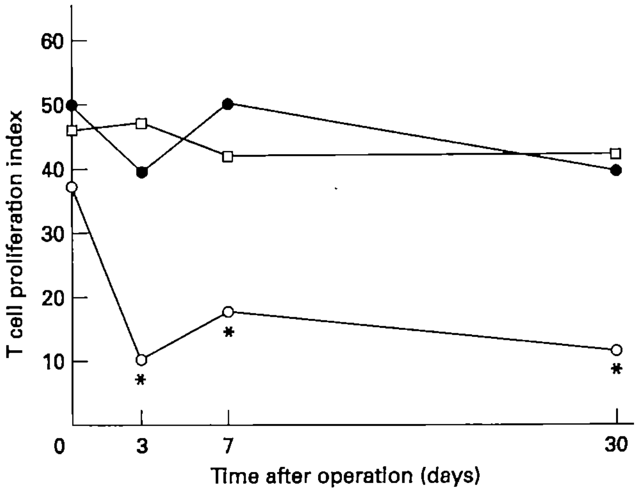

Fig. 1 Median lymphocyte proliferation (c.p.m. × 10^3) in 19 patients transfused with whole blood (○), 15 transfused with leucocyte-depleted blood (●) and 26 having no transfusion (□). *$P < 0{\cdot}01$ (whole blood transfusion *versus* transfusion with leucocyte-depleted blood and no transfusion, Mann–Whitney *U* test)

Table 1 Characteristics of patient groups

	Non-transfused	Filtered whole blood	Whole blood
No. of patients	26	15	19
Sex ratio (M:F)	18:8*	5:10	6:13
Median (range) age (years)	62 (36–81)	68 (36–95)	63 (26–84)
Diagnosis			
Malignancy	22	13	14
Other	4	2	5
Operative procedure			
Right hemicolectomy	4	3	2
Left hemicolectomy	1	1	2
Sigmoid resection	10	1	4
Anterior resection	4	3	3
Other resection	2	0	1
Hartmann's operation	1	2	0
Colostomy	1	1	0
Proctocolectomy	0	1	3
Abdominoperineal excision	3	3	4
Median (range) duration of surgery (min)	120 (70–260)†	180 (70–320)	150 (60–320)
Abdominal wound infection	0	0	7‡
Intra-abdominal abscess	0	0	2

*$P < 0{\cdot}05$ (non-transfused *versus* transfused patients, Fisher's exact test); †$P < 0{\cdot}05$ (non-transfused *versus* transfused patients, Mann–Whitney *U* test); ‡$P < 0{\cdot}01$ (whole blood transfusion *versus* filtered blood transfusion and no transfusion, Fisher's exact test)

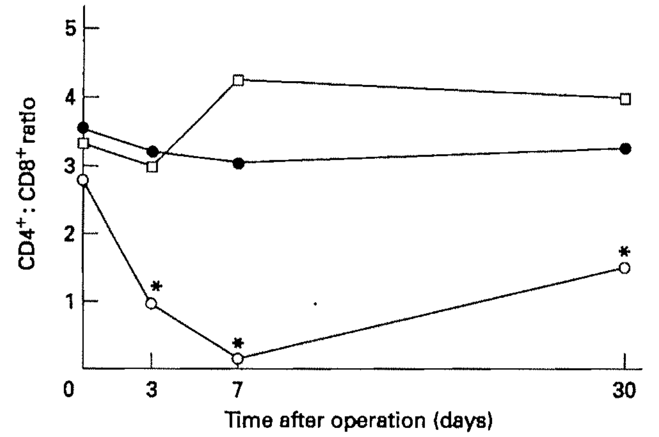

Fig. 2 Median CD4$^+$: CD8$^+$ ratio in 19 patients transfused with whole blood (○), 15 transfused with leucocyte-depleted blood (●) and 26 having no transfusion (□). *$P < 0{\cdot}01$ (whole blood *versus* leucocyte-depleted blood transfusion and no transfusion, Mann–Whitney *U* test)

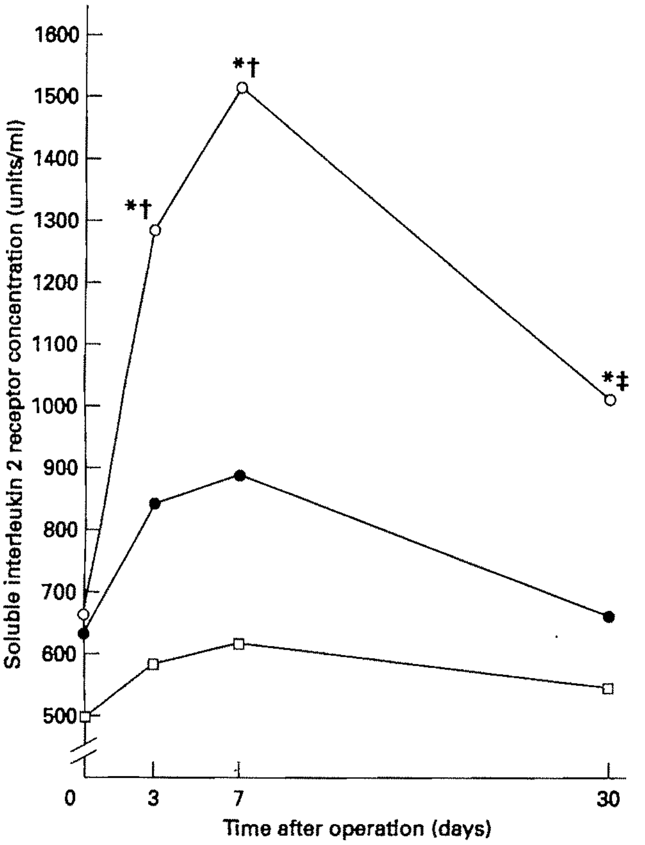

Fig. 3 Median soluble interleukin 2 receptor levels in 19 patients transfused with whole blood (○), 15 transfused with leucocyte-depleted blood (●) and 26 having no transfusion (□). *$P < 0{\cdot}01$ (whole blood *versus* leucocyte-depleted blood transfusion and no transfusion, Mann–Whitney *U* test); †$P < 0{\cdot}01$ (days 3 and 7 *versus* day 0); ‡$P < 0{\cdot}05$ (day 30 *versus* day 0) (Wilcoxon rank sum test)

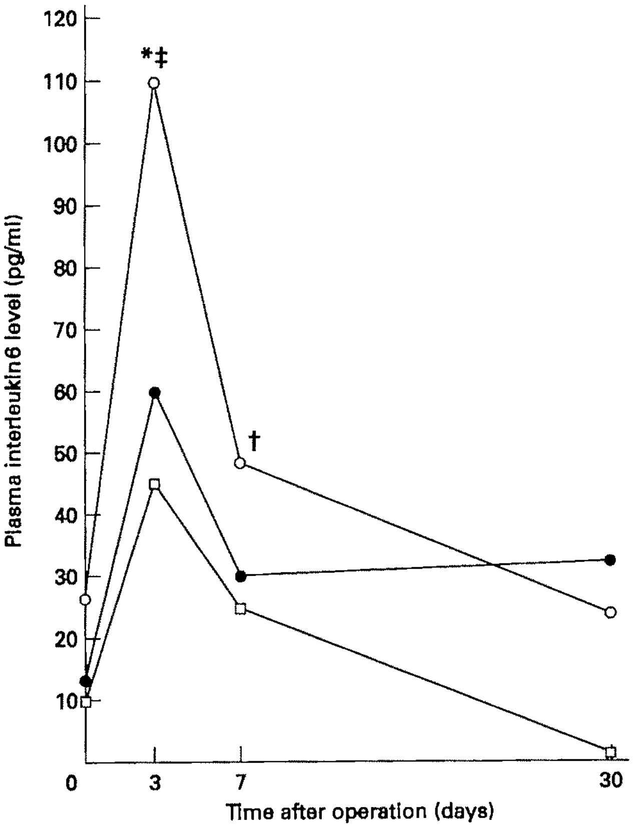

Fig. 4 Median plasma interleukin 6 levels in 19 patients transfused with whole blood (○), 15 transfused with leucocyte-depleted blood (●) and 26 having no transfusion (□). *$P < 0{\cdot}01$, †$P < 0{\cdot}05$ (whole blood *versus* leucocyte-depleted blood transfusion and no transfusion, Mann–Whitney *U* test); ‡$P < 0{\cdot}01$ (day 3 *versus* day 0, Wilcoxon rank sum test)

cantly higher than that in the other groups 30 days after operation (*Fig. 3*). It was only the patients transfused with whole blood who developed infectious complications (*Table 1*), but there was no difference in sIL-2R levels between patients with and without infection at days 3 and 7 after operation. However, at day 30 after surgery patients who had developed infectious complications still had high levels of sIL-2R, whereas the value in non-infected patients had returned to levels no different from those found before operation.

The level of plasma IL-6 in healthy volunteers is below the detection limit in the authors' laboratory[19]. Preoperative values of IL-6 were similar in all three groups (*Fig. 4*). On day 3 after surgery a significant increase ($P < 0{\cdot}01$) was noted in the group transfused with whole blood compared with the slight and non-significant increase in the non-transfused and leucocyte-depleted group (*Fig. 4*). On day 7 the level markedly decreased in the group transfused with whole blood, but was still significantly higher ($P < 0{\cdot}05$) than that in the other groups. By day 30 the level had returned to the preoperative value in all three groups. With regard to whole blood transfusion there was no significant difference in the level of IL-6 between patients with and without infection.

Discussion

The present study demonstrates that transfusion with whole blood in elective colorectal surgery is followed by a significant depression in immunocompetence, and that this depression is attenuated by the use of leucocyte-depleted blood.

Immunosuppression following allogeneic blood transfusion is additive to the known effects of surgery and anaesthesia[16,17,21]. Furthermore, underlying disease can influence immunocompetence[17]. However, no differences in underlying disease were present in the three groups of patients in the present study, and in particular the frequency of malignant disease was similar. Consequently the preoperative values for all immunological parameters studied were also similar. In the non-transfused patients and in those transfused with leucocyte-depleted blood there were few postoperative changes in the proportion of $CD4^+$ and $CD8^+$ cells or in the proliferation of lymphocytes. In the non-transfused group no change in the level of sIL-2R was observed. In the group transfused with leucocyte-depleted blood there was a transient but non-significant increase in the level of sIL-2R. This may be a result of surgery, but the difference from that found in non-transfused patients may indicate that, besides leucocytes, there may be other elements in blood that are immunosuppressive[17].

It has been suggested that the immunosuppressive effect of blood transfusion is partially attributable to haemorrhage, reperfusion and hypotension[22]. However, in the present study the potential effects of haemorrhage were overshadowed by the immunosuppressive effects of whole blood transfusion, because patients in the two transfused groups received the same amount of blood, as indicated by the equal distribution of blood loss during surgery.

The decision to compare the effects of whole blood transfusion with leucocyte-depleted blood was intended to ensure that one blood product with all elements of blood was compared with another almost completely depleted of white cells but with the same content of red blood cells and plasma. This made it possible to discriminate between the effect of plasma and that of plasma and leucocytes. As suggested by Blumberg and Heal[23], it cannot be excluded that plasma is also required in addition to leucocytes to increase the immunosuppressive effects. As all units of blood were less than 3 weeks old, the spontaneous release of immunosuppressive agents was minimized[24], and other possible effects of storage were assumed to be the same in the two groups receiving transfusion.

Although buffy coat-depleted blood (SAG-M) and plasma-reduced whole blood are most frequently used for transfusion, whole blood is still used in many countries. Furthermore, the leucocyte concentration in plasma-reduced whole blood and SAG-M blood is 100 and 30 per cent respectively of that in whole blood, and evidence has emerged to suggest that these transfusions also lead to immunosuppression[17].

The most impressive change in the present study was the significant decrease in T cell proliferation and the $CD4^+:CD8^+$ ratio, as well as the increase in the levels of sIL-2R and IL-6 in patients transfused with whole blood compared with those in patients transfused with leucocyte-depleted blood. Moreover, patients receiving whole blood developed significantly more infectious complications than those transfused with leucocyte-depleted blood. The mechanism whereby leucocytes mediate these effects is not understood. However, the suppressive effect of blood transfusion on allograft rejection and the induction of human leucocyte antigen alloantibodies are also dependent on leucocytes in transfused blood[25].

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Editor's announcement

Illustrations in colour

The Journal does not contain many illustrations in colour at present, probably because authors are usually requested to make a contribution towards the cost of colour reproduction. This cost is substantial, amounting to approximately £500 per figure at current rates. In association with the publishers, Blackwell Science Ltd, The British Journal of Surgery Society is keen to increase the number of colour illustrations in the Journal. The use of colour is particularly appropriate for operative photographs (whether open operation or laparoscopy), resection specimens and especially photomicrographs. To encourage the submission of suitable illustrations in colour, authors' charges will be waived. Three high-quality prints of each figure should be submitted.

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British Journal of Surgery 1996, **83**, 978–980

Prospective randomized controlled study of clinical function and anorectal physiology after low anterior resection: comparison of straight and colonic J pouch anastomoses

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Clinical function and anorectal physiology were studied prospectively in patients with rectal cancer after low anterior resection, randomized to either a straight anastomosis or an 8-cm colonic J pouch anastomosis. Sixteen patients (mean(s.e.m.) age 61·2(3·2) years; ten men, six women) had a straight anastomosis and 17 (mean(s.e.m.) age 61·2(3·8) years; six men, 11 women) a colonic pouch anastomosis. At 1 year after low anterior resection, a bowel function questionnaire was administered and anorectal physiology tests were performed. Patients with a straight anastomosis had significantly more frequent stools (median 6 (range 3–7) daily) compared with those who had a pouch (median 3 (range 2–7) daily; $P = 0{\cdot}02$). A frequent sensation of incomplete defaecation was found in three patients with a straight anastomosis compared with ten who had a pouch anastomosis ($P = 0{\cdot}02$). The mean resting anal pressures were lower after colonic pouch anastomosis ($P = 0{\cdot}049$) but there were no differences in anal squeeze pressure, rectal sensation, volume of first sensation and compliance between the two groups. The decreased stool frequency with an 8-cm colonic pouch was not associated with measured improvements in rectal reservoir function. It is possible that reversed propulsive activity may be important in smaller colonic J pouches.

The problem with low anterior resection is that postoperative bowel function may be less than ideal. Although rectal cancer clearance is effective with acceptable risks[1–3], some patients are disturbed by excessive stool frequency and soiling[4–6]. The mean stool frequency may range from 1·4 to 14·1 times daily[4,7]. Faecal continence may be compromised in 13–80 per cent[2,4,7]. Poor function is related to the amount of rectum resected[7–12]. This in turn relates to the eventual reservoir function of the neorectum, consisting of proximal colon anastomosed to the rectal stump[9]. Being less compliant[4,9–13], stools are stored less efficiently.

To increase the reservoir capacity of the neorectum, a colonic pouch can be constructed proximal to the colorectal anastomosis[14]. This has resulted in decreased stool frequency, but sometimes at the risk of defaecation problems[15–19]. The physiological understanding for ideal colonic pouch design has yet to be clarified. An 8-cm colonic J pouch has previously been shown to give good function[16]. The clinical function and anorectal physiology of such a colonic pouch were compared with those of straight anastomosis of the descending colon to the rectal stump after low anterior resection.

Patients and methods

A prospective randomized study was performed from January 1991 to July 1995. Thirty-three consecutive patients with curative surgery performed for adenocarcinoma of the mid or lower rectum consented to recruitment. They were randomized to either straight anastomosis or colonic pouch anastomosis by drawing sealed envelopes. All patients underwent a standardized extended low anterior resection. The left colon was mobilized to proximal to the splenic flexure. The inferior mesenteric artery was ligated proximal to the left colic artery. The rectum was dissected down to the pelvic floor with total clearance of the mesorectum. An RL 30 transverse stapler (Ethicon, Somerville, New Jersey, USA) was applied at or just proximal to the anorectal junction and the rectum was removed. In patients who had a straight anastomosis, the descending colon was anastomosed to the anorectal stump by the double cross stapling technique[20], using a CDH 33 intraluminal stapler (Ethicon). In other patients an 8-cm J pouch was constructed from the descending colon using a PLC 75 linear cutting stapler (Ethicon), as previously described[16]. The colonic pouch was then anastomosed to the anorectal stump by a similar double stapling method. All patients had a defunctioning loop ileostomy, which was subsequently closed 3 months later.

After operation, the patients were followed up at 3-month intervals. Patients with Dukes C lesions underwent adjuvant chemotherapy and radiotherapy (4500–5000 cGy in 28 fractions over 5 weeks). A bowel function questionnaire was administered 1 year after low anterior resection. At the same time, anorectal manometry was performed using a microcapillary perfusion system (Synectics, Stockholm, Sweden). A balloon in the rectum was perfused with water at a rate of 60 ml/min. The volume of first sensation was taken when the patient first detected any sensation of difference. The maximum tolerable volume was taken when the patient could no longer tolerate further rectal distension.

Statistical significance was calculated using the Mann–Whitney U, χ^2 or Pearson correlation tests where appropriate.

Results

Sixteen patients (mean(s.e.m.) age 61·2(3·2) years, ten men, six women) were randomized to straight anastomosis and 17 (mean(s.e.m.) age 61·2(3·8) years; six men, 11 women) to colonic pouch anastomosis. Dukes stage was A (two patients), B (seven) and C (seven) in the straight anastomosis group, and A (one), B (seven) and C (nine) in the colonic pouch anastomosis group. There was no significant difference in the number of patients with Dukes C lesions in each group, who received adjuvant chemoradiotherapy.

Paper accepted 20 November 1995

Clinical function

No significant difference was found in height of the anastomosis from the anal verge in the two groups of patients (mean(s.e.m.) 3·1(0·1) *versus* 3·0(0·2) cm for straight *versus* pouch anastomosis). There was no complication, including clinical anastomotic leak, after low anterior resection or subsequent closure of the ileostomy. At a mean(s.e.m.) follow-up of 32·5(2·6) months, there were no local or distant cancer recurrences. The functional results are shown in *Table 1*. Patients with a straight anastomosis had significantly more frequent stools than those with a pouch ($P = 0{\cdot}02$). However, there were significantly fewer in the straight anastomosis group who had frequent sensations of incomplete defaecation than in the colonic pouch anastomosis group ($P = 0{\cdot}02$).

Anorectal physiology

The anorectal physiology results are shown in *Table 2*. Except for a significantly lower mean resting pressure in the patients with a colonic pouch anastomosis ($P = 0{\cdot}049$), there were no differences in the other parameters measured. The mean resting pressures were not significantly related to any differences in the age and sex of the patients. There were no significant correlations between the volume of initial sensation, maximum tolerable volume and rectal compliance, and the stool frequency and urgency.

Table 1 Functional results after low anterior resection with straight and colonic pouch anastomosis

	Straight ($n = 16$)	Colonic pouch ($n = 17$)	P
Median (range) stool frequency (per 24 h)	6 (3–7)	3 (2–7)	0·02*
Stool consistency			0·6†
Hard	1	2	
Soft	10	12	
Liquid	5	13	
Impaired social life	2	0	0·3†
Occasional incontinence	1	1	0·8†
Pad required	1	1	0·1†
Urgency (<15 min)	5	1	0·2†
Sensation of incomplete defaecation	3	10	0·02†
Antidiarrhoeal medication	6	5	0·6†

*Mann–Whitney *U* test; †χ^2 test

Discussion

These results confirm that patients with a colonic pouch anastomosis have less distressingly frequent stools than those with a straight anastomosis, after low anterior resection with anastomoses at or just above the anorectal junction. The patients with a colonic pouch had a median of 3 stools daily compared with 6 for those with a straight anastomosis. Fewer patients with a colonic pouch anastomosis were troubled by urgency to defaecate, but this was not statistically significant. Only one patient from each group had occasional liquid faecal soiling, which was satisfactorily managed by wearing a perineal pad. These results were assessed at 1 year, when any improvements in function were expected to have stabilized[4]. These findings were consistent with other reports of randomized prospective controlled data[16,17], as well as large series with long follow-up[18]. However, a frequent sensation of incomplete defaecation was more common after colonic pouch anastomosis (ten patients) than after straight anastomosis (three). None of the patients required suppositories or enemas to evacuate. More severe difficulties in evacuation and stasis were encountered with larger (10-cm) colonic pouches[21] and when the sigmoid colon was used in pouch construction[18]. Postoperative adjuvant chemoradiotherapy may influence the bowel function[22] but there was no significant difference between the number of patients undergoing adjuvant therapy between the two groups.

There were no differences in rectal physiology (volume of initial sensation, maximum tolerable volume and compliance) measured between the two groups. The stool frequency and urgency also did not correlate with these parameters. Increased frequency and urgency after low anterior resection have been partly attributed to loss of the reservoir capacity of the rectum[9,23]. Improved function with a colonic pouch was attributed to enhanced rectal volumes and compliance, as demonstrated in previous studies[17,21]. However, the colonic pouches tested in those studies were of a larger size (10 cm) than those used in the present patients. There were no differences in the measured reservoir function between a straight segment of descending colon (which is more distensible than sigmoid colon which might have been used by others) and a small 8-cm J colonic pouch. Smaller colonic pouches were preferred because the risk of evacuation problems was less[16]. It is possible that the improved function from smaller volume colonic pouches may have resulted from some reversal of propulsive movements in the J segment. Further studies are needed to clarify this postulation. The authors cannot account for the lower resting anal pressures in patients with a colonic pouch anastomosis,

Table 2 Anorectal physiology after low anterior resection with straight and colonic pouch anastomosis

	Straight ($n = 16$)	Colonic pouch ($n = 17$)	P
Mean resting anal pressure (mmHg)	71·1(5·8)	55·0(6·7)	0·049*
Maximum squeeze anal pressure (mmHg)	152·7(14·5)	143·5(18·4)	0·5*
Physiological anal length (cm)	1·9(0·2)	1·9(0·3)	0·8*
Volume of initial rectal sensation (ml)	66·3(6·6)	65·4(5·7)	1*
Maximum tolerable rectal volume (ml)	174·8(25·7)	149·2(12·2)	1*
Rectal compliance (ml/mmHg)	3·3(0·6)	3·8(0·6)	0·3*
Rectosphincteric inhibitory reflex present	6	9	0·4†

Values are mean(s.e.m.). *Mann–Whitney *U* test; †χ^2 test but a similar result was obtained in a previous randomized study[17]. However, further data are required to ascertain the true significance of this finding.

It is concluded that the 8-cm colonic J pouch decreases stool frequency but gives increased minor defaecation problems 1 year after low anterior resection. The anorectal physiological aspects of such surgery need further study and understanding. This may help to achieve an ideal balance between postoperative stool frequency/urgency and defaecation problems. The resulting refinements in colonic pouch size and design might perhaps lead to improvement in postoperative function.

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British Journal of Surgery 1996, 83, 981

Surgical workshop

Colonic parastomal hernia repair by translocation without formal laparotomy

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The most frequent complication of colostomy is parastomal hernia. Such a hernia may be caused by poor surgical technique, infection, incorrect location or too large a hole (early hernia), or by high intra-abdominal pressure due to obesity, constipation, prostatism or chronic cough (late hernia)[1]. According to Rubin *et al.*[2], the risk of recurrence after parastomal hernia repair is considerable and is higher for fascial repair (76 per cent) than for stoma relocation (33 per cent). However, complications are more common after stoma relocation (88 per cent) than following fascial repair (50 per cent). This high rate reflects incisional hernia, which develops in 52 per cent of patients. In the study of Rubin *et al.*[2], stoma relocation involved laparotomy in all cases. In 1967, Turnbull developed a method wherein the ileal stoma could be relocated without the need for a formal laparotomy. In 1978, Taylor, Rombeau and Turnbull[3] reported experience with transperitoneal ileal stoma relocation without formal laparotomy in 19 patients. Kaufman[4] in 1983 described a similar technique of translocation of an ileal stoma to the opposite side of the abdomen.

Surgical technique

On the basis of Turnbull's method, the senior author (J.M.L.) has developed a new technique for relocation of a colonic stoma with parastomal hernia without formal laparotomy. For anatomical reasons the translocation has to be made on the same side of the abdomen. A circumstomal fusiform incision is made in the skin. The original primary stoma is closed with silk stitches, the first and the last of which are not cut so that the threads remain long; the stoma is then dissected and reintroduced inside the peritoneal cavity. A disc of skin is dissected 6 cm above or below the original primary colostomy. The fascia of the original primary colostomy is then closed with a no.1 polypropylene suture, but the stitches are not tied. The threads are secured with a Kocher or similar clamp. These threads are then pulled firmly, so that the fascia moves from the new site to the primary colostomy site. Next the fascia is incised where the new colostomy is to be placed (*Fig. 1*). This method ensures a large separation between both fascial sheath incisions. This allows safe closure of the original colostomy fascia, without any tension, after the terminal portion of the colon has been brought through the newly created stoma site using the two long threads. No more than 1 cm of the terminal portion of the colon should be excised; otherwise the mesocolon would have to be trimmed, which could lead to difficulty with irrigation.

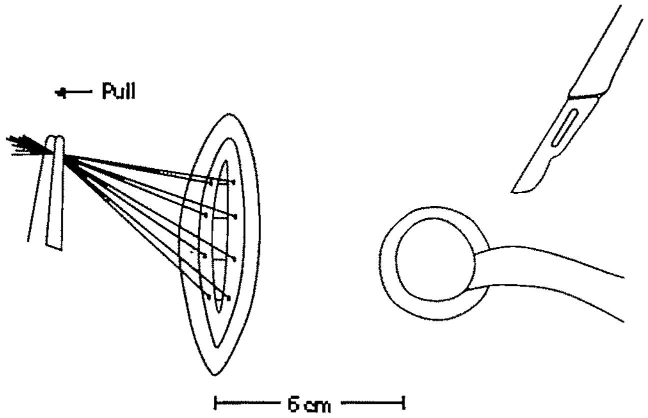

Fig. 1 As the closing stitches of the original colostomy are pulled, the fascia of the new colostomy location is incised

Between November 1992 and June 1995, 11 repairs of parastomal hernia by translocation of the colostomy without formal laparotomy were performed in 11 patients. The patients were eight women and three men aged 42–86 (mean 63) years. Follow-up ranged from 2 to 36 months; no wound infection or other complication was observed. Up to now there has been no recurrence. No intra-abdominal adhesions of the terminal colon have been encountered in any patient; this may be due to their self-dissection secondary to the continuous entrance and exit from the hernial sac.

In the authors' experience the advantages of this technique are reduced morbidity, less surgical trauma and postoperative pain, shorter operating time (about 1 h), reduced convalescence and lower risk of infection.

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Paper accepted 18 October 1995

British Journal of Surgery 1996, 83, 982–985

Iron status following trauma, excluding burns

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Serum concentration of iron, transferrin saturation and total iron binding capacity (TIBC) were measured on days 1, 2, 3, 5, 7, 10 and 13 in 36 Thai patients with trauma (burns excluded) to determine temporal changes in iron metabolism. Throughout the study profound hypoferraemia was observed in association with decreased transferrin saturation. TIBC, in contrast, did not differ significantly from that in controls. These findings confirm previous reports which describe altered iron metabolism in association with an adverse event, a response known as 'stress hypoferraemia', and extends these observations to non-burned patients with trauma. The degree of hypoferraemia in patients in this study was not related to sepsis, Injury Severity Score, volume of blood transfused or surgery, suggesting that hypoferraemia following trauma is an independent event. The recognition of rapid and prolonged iron sequestration provides insight into the clinical condition of patients with trauma.

Iron metabolism is a tightly controlled process important in erythropoiesis, in the production of bactericidal products, in the promotion of cell growth and differentiation, and in nitric oxide metabolism[1–3]. Alteration of iron metabolism occurs in many diseases and is a sensitive indicator of illness[1,2]. In particular, acute conditions such as infectious disease, surgery, fractures and myocardial infarction are characterized by a profound and prolonged hypoferraemia which lasts well beyond the recuperation period[2,4]. This process, known as 'stress hypoferraemia' or 'iron withholding', may be a physiological response which benefits the host by restricting microbial access to iron[2,5]. Macrophages may play a role in the iron sequestration of stress hypoferraemia by expressing cell-surface transferrin receptors[6]. Transferrin receptors, under the influence of specific environmental stimuli, bind and internalize circulating iron complexes[6].

Non-burned patients with trauma have a wide range of physiological responses[7–9], one of which involves altered iron regulation[10]. To characterize the changes in iron metabolism, serum iron concentration, transferrin saturation and total iron binding capacity (TIBC) were serially determined over 2 weeks following admission for non-burn trauma.

Patients and methods

Patients of Thai ethnic origin with trauma were selected for the study following admission to one of three hospitals in Bangkok, Thailand: Siriraj Hospital (Mahidol University), Phramongkutklao Hospital (Royal Thai Army) and the Police Hospital. Thirty-six consecutive patients with trauma aged 18–50 years with an Injury Severity Score (ISS)[11] greater than 20 were enrolled after obtaining informed consent. Ethical considerations, as outlined by the US Army Human Use Research Review Board guidelines and each individual hospital ethical committee, were followed.

Patients were evaluated in the emergency room to determine whether enrolment criteria were met and a final decision was made after any emergency surgery had been performed with accurate assessment of all injuries. On admission to the study patients were reviewed daily by both research and clinical personnel. Patient records included vital signs, requirement for ventilatory assistance, nutritional status, all medications (including antibiotics, steroids and resuscitation drugs) and intravenous fluid requirements. Patient outcome was graded as uneventful (no infection), sepsis (mild infection) or sepsis syndrome (septic organ failure), as described previously[12]. Patients were followed until discharge or death.

All necessary surgical intensive care support was given to patients, including surgical intervention, fluid resuscitation, respiratory assistance and parenteral nutrition. All patients were initially given empirical antibiotic coverage, which usually consisted of a third-generation cephalosporin and was either discontinued or changed to oral administration if no infection developed. If a patient developed signs of sepsis or sepsis syndrome, antibiotic coverage was amended, based on the presumed source until culture results were available.

Control patients consisted of 30 uninjured healthy volunteers of Thai ethnic origin from the laboratory and hospital community without evidence of iron overload.

Blood was obtained from patients on days 1, 2, 3, 5, 7, 10 and 13 after hospital admission. Some 10 ml of venous blood was drawn aseptically into a sterile syringe and transferred into an

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Presented in part to the 15th annual conference on Shock in Point Clear, Alabama, June 1992

The opinions and assertions contained in this article are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense

Paper accepted 18 October 1995

iron-free tube. Samples were transported in a chilled container at 4–10°C. Specimens were processed immediately on arrival at the laboratory.

Serum concentration of iron, TIBC and transferrin saturation were measured by standard methods outlined by the International Committee for Standardization in Hematology[13].

Data were double entered into a computerized database (DBASE IV; Ashton-Tate Corporation, Torrance, California, USA) and cross-checked against original data-entry sheets before analysis. All analyses were performed on a 486 IBM-compatible computer using Statgraphics, version 4 (Statistical Graphics Corporation, Gaithersburg, Maryland, USA). Patient and control values were compared with the non-parametric Mann–Whitney *U* test for two samples.

Results

A total of 36 patients with trauma, of mean(s.e.m.) age 28(4) years were enrolled in the study (*Table 1*). There were 32 blunt and four penetrating injuries. Clinical outcome was uneventful in 20 patients; nine developed sepsis and seven had sepsis syndrome. Organ involvement and bacteria isolated from patients who developed sepsis syndrome are shown in *Table 2*. The control group consisted of 26 male and four female healthy volunteers of mean(s.e.m.) age 28(0·5) years.

Serum iron

Serum iron concentration was significantly decreased on all days after injury. The lowest values occurred on days 2 and 3 (*Fig. 1*). Although the level of serum iron gradually increased after day 3, values remained significantly lower up to day 13, compared with control values. The degree of hypoferraemia was not related to clinical course, ISS, surgery or volume of blood transfused.

Table 1 Patient details

Total no. of patients	36
Sex ratio (M:F)	32:4
Mean(s.e.m.) Injury Severity Score	30(4)
Clinical course	
Uneventful	20
Sepsis	9
Sepsis syndrome	7
No. of transfused units*	
0	10
1–5	15
>5	11
No. undergoing surgery	30
Mean(s.e.m.) (range) hospital stay (days)	42(23) (7–123)
Mean(s.e.m.) (range) stay in intensive care (days)	13(11) (2–35)

*Volume of blood transfused within the initial 48 h of admission

Table 2 Patients who developed sepsis syndrome

Patient no.	Organism isolated	Organ failure	Outcome
1	*Klebsiella pneumoniae*	Respiratory	Survived
2	*Pseudomonas aeruginosa*	Renal, respiratory	Died
3	*Escherichia coli*	Hepatic	Survived
4	None	Renal	Survived
5	None	Renal, hepatic	Died
6	*Klebsiella pneumoniae*	Respiratory	Survived
7	None	Renal	Died

All patients had been involved in road traffic accidents

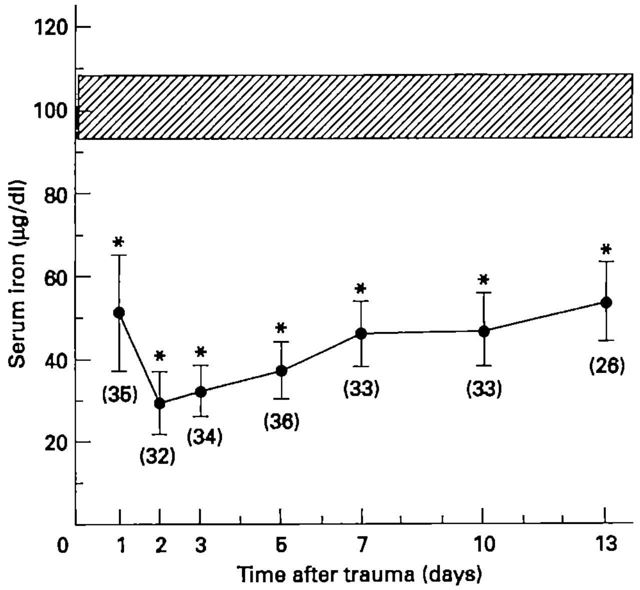

Fig. 1 Mean(s.e.m.) levels of serum iron in patients with trauma. Patient numbers are given in parentheses. The 95 per cent confidence interval for controls (93–109 µg/dl) is shown in the hatched box. *$P<0·001$ *versus* control value (Mann–Whitney *U* test)

Table 3 Mean values of transferrin saturation and total iron binding capacity in patients and controls

		Days following trauma						
	Controls	1	2	3	5	7	10	13
Transferrin saturation (%)	35 (32–38)	19*	10*	11*	13*	13*	16*	18*
TIBC (µg/dl)	292 (276–308)	272	288	287	288	305	323	296

Values in parentheses are 95 per cent confidence intervals. TIBC, total iron binding capacity. *$P<0·001$ *versus* control (Mann–Whitney *U* test)

Transferrin saturation

Transferrin saturation was decreased on all days. The lowest values occurred on days 2 and 3 (*Table 3*). Similar to serum iron concentration, transferrin saturation gradually increased after day 3 but remained significantly lower at day 13 compared with that in controls. Transferrin saturation was not related to clinical course, ISS, surgery or volume of blood transfused.

Total iron binding capacity

TIBC did not differ significantly from the control values (*Table 3*).

Discussion

This study shows that non-burned patients with trauma have a rapid and profound hypoferraemia and decreased transferrin saturation. TIBC, in contrast, was not significantly different from that in controls. Changes in serum iron concentration and transferrin saturation were not related to development of infection, ISS, blood transfusion or surgery. These observations are consistent with previous reports describing severe hypoferraemia in association with adverse conditions[2,5] and are extended to patients with trauma excluding burns.

Serum iron concentration, transferrin saturation and TIBC are the most commonly used parameters to evaluate iron status and define anaemic states[1]. The patients in this study exhibited low serum levels of iron, low transferrin saturation and normal TIBC, a combination inconsistent with either iron-deficient anaemia or anaemia of chronic disease[1]. This suggests that the pathophysiology of hypoferraemia following trauma may represent a secondary anaemia which differs from that of chronic disease and may be associated with normal red blood cell indices and haemoglobin concentration[2,4].

Acute conditions such as infectious disease, myocardial infarction, fractures, surgical procedures, fever and endotoxaemia are characterized by a rapid drop in serum iron concentration and increased iron storage[2,4,14,15]. Because only the iron bound to transferrin in circulation is accessible to pathogens, the rapid drop in iron concentration is considered beneficial to the host by limiting iron availability to potential bacterial invaders[2,5]. This protective mechanism has been termed 'nutritional immunity' and may be of particular importance in the suppression of bacterial virulence early after exposure, before specific cellular and humoral-mediated immunity can respond[16]. A rapid and prolonged hypoferraemia would be especially beneficial to immunosuppressed patients with trauma who are at increased risk of developing septic complications from Gram-negative organisms[7]. The major organisms responsible for Gram-negative sepsis (*Escherichia coli*, *Klebsiella* species and *Pseudomonas aeruginosa*) require iron for proliferation and synthesize powerful siderophores to extract iron from the host[17].

Stress hypoferraemia may be mediated by macrophages, cells that maintain iron homoeostasis by serving as the major iron storage organ in the body[6]. The interplay between macrophages and iron metabolism is under the influence of specific environmental factors such as interleukin (IL) 1 and tumour necrosis factor (TNF) which regulate macrophage expression of transferrin receptors, membrane proteins involved in iron uptake and storage[6]. IL-1 and TNF stimulate macrophage transferrin receptor expression and play a role in the hypoferraemia observed in sepsis and chronic disease[6]. In patients with trauma, IL-1 and TNF are readily detected[8,9] and may act as triggers that initiate massive iron uptake by stimulating increased expression of the macrophage transferrin receptor. Indeed, experimental studies have shown that intravenous administration of IL-1 alone produces a severe and long-lasting hypoferraemia[16].

Once iron uptake and storage has been triggered in macrophages, transferrin receptor expression is regulated under an unusual positive feedback loop: internalization of iron–transferrin complexes upregulates the expression of transferrin receptors, promoting further iron uptake[6,18,19]. The significance of the positive feedback mechanism in controlling macrophage transferrin receptor expression is unknown, but indicates tight control of iron metabolism. More importantly, a positive feedback loop may account for the prolonged hypoferraemia, beyond the recuperation period, observed in patients with trauma and other critical illness. Hypoferraemia in patients with uncomplicated fractures or following a single dose of endotoxin persists for weeks[4,12].

Recognition of changes in iron status provides further insight into the clinical status of multiply injured patients. The response observed in non-burn trauma appears identical to the prolonged drop in serum levels of iron following operative procedures in uninjured patients[2]. The importance of hypoferraemia as a host defence mechanism in uninjured patients following operation is supported by reports of increased virulence of *E. coli* infections in animal models if iron availability is increased[20–22]. Parenteral administration of iron might enhance bacterial multiplication in surgical wounds[2]. Iron administration in humans is associated with increased rates of neonatal Gram-negative sepsis and reactivation of malaria, brucellosis and tuberculosis[2].

In normal persons the unsaturated iron binding proteins transferrin and lactoferrin limit the amount of free iron in tissue fluids to virtually zero to maintain the normal antibacterial properties of blood[17]. Because readily available iron present in blood products, blood substitutes (modified haemoglobin) and parenteral nutrition can abolish these protective mechanisms, limited or modified use of these treatment modalities has been advocated[23]. Studies in animals have shown that haemoglobin and other iron-containing substances can promote bacterial growth and render non-fatal bacterial infections fatal[23]. Another theoretical consequence of administering additional iron might include alterations in nitric oxide metabolism[3]. Patients with non-burn trauma are unique because injured tissue provides two additional sources of readily available iron: haemoglobin from lysed red blood cells and iron release during breakdown of necrotic tissue. Minimizing iron availability in patients with trauma by rapid surgical treatment of large haematomas or massively contused muscle may be beneficial[17,23].

Acknowledgements

The authors thank Prappussorn Kongcharoen, Kosol Yongvanitchit and Pongsri Tongtawe of the Armed Forces Research Institute of Medical Sciences (AFRIMS) for laboratory assistance. They also thank Suchada Chinaworapong (AFRIMS), Prisina Benjamit, Nonglak Peunchampoo, Prachid Saratapun (Siriraj Hospital), Major Somchit Sukwatanakul and Captain Somraudee Charauchinda (Phramongkutklao Hospital) for clinical assistance. Saowaluck Jirakul provided secretarial assistance.

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British Journal of Surgery 1996, 83, 986

Short note

Laparoscopic oöphorectomy: description and report of an initial series

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Considerable controversy still exists as to the most appropriate adjuvant therapy for breast cancer. Hormonal, chemotherapeutic and radiotherapy regimens are appropriate in various circumstances. While oöphorectomy offers similar survival advantages to chemotherapy[1–3], it has largely been supplanted by the latter as primary adjuvant therapy mainly because of the necessity for laparotomy or radiotherapy with attendant morbidity and side-effects. The advent of laparoscopic oöphorectomy confers considerable potential advantages over other methods of oöphorectomy: laparotomy, radiotherapy and drugs. The technique and initial experience in 56 patients who underwent laparoscopic oöphorectomy are described here.

Patients and methods

Fifty-six premenopausal women were deemed suitable for laparoscopic oöphorectomy. All had routine preoperative assessment for metastatic disease and oestrogen receptor levels were measured. Patients were included in the study after primary definitive breast cancer surgery (either segmentectomy or mastectomy plus axillary clearance). All patients received counselling from the surgical team and breast-care nurses, and gave informed consent.

Operative technique

A standard technique was utilized. After bladder catheterization under general anaesthesia a pneumoperitoneum was produced by introducing a subumbilical Veress needle or direct cut down. A 10-mm subumbilical cannula was then placed for the camera, and two further 12-mm cannulas were situated in the right and left iliac fossae. After identification of the ovaries, the tubo-ovarian pedicle was clamped and divided using an Endo-GIA stapling device (AutoSuture, Norwalk, Connecticut, USA). Two firings of the Endo-GIA were usually required on each side. The ovaries were then removed with an endograsping forceps and sent for histological assessment.

Results

Fifty-two of the 56 patients undergoing oöphorectomy had primary operable disease and four recurrent carcinoma. All were premenopausal with a mean age of 42 (range 34–54) years. Thirteen patients had stage 1 disease and 36 stage 2, three patients had stage 3 and four had recurrent disease.

Oöphorectomy was performed a mean of 9 days after operation for primary breast cancer. Median post-operative stay was 2 (range 1–6) days. Mean operating time was 25 (range 25–45) min.

Serious complications occurred in two patients. The first patient in the series required conversion to laparotomy owing to difficulty in visualization and haemorrhage, which necessitated transfusion of 2 units of blood. A second patient had a postoperative haemorrhage from the left iliac fossa port site, which settled with conservative treatment but also required a 2-unit transfusion. Menopausal symptoms were minimal[4].

All patients received postoperative adjuvant tamoxifen, and 54 are alive and well at a median follow-up of 14 (range 1–40) months. One patient has died from metastases, and a second has shown clear-cut progression of disease.

Discussion

Careful analysis has shown that ovarian ablation produces valuable reductions in death and recurrence from breast cancer. This benefit is maintained beyond 10 years of follow-up[1]. The ability to perform laparoscopic oöphorectomy with relatively few complications has been established by this report, but this is not a controlled trial showing improvement over other forms of therapy in breast cancer. It confirms the feasibility of a combination of laparoscopic oöphorectomy and tamoxifen with minimal side-effects in the treatment of premenopausal breast cancer. Other reports suggest that long-term follow-up will demonstrate increased benefits from oöphorectomy at all stages of disease[4]. It should be considered as a front-line combination in the management of premenopausal women with breast cancer.

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Paper accepted 7 September 1995

British Journal of Surgery 1996, 83, 987–988

Short note

Initial experience with endoscopic retroperitoneal adrenalectomy

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Adrenalectomy is conventionally performed using a transabdominal or posterior approach[1,2] Laparoscopic adrenalectomy has advantages associated with minimally invasive surgery. Initial experience was obtained using a transabdominal approach[3,4], but retroperitoneal endoscopic adrenalectomy has recently been described[5–8] and the present report discusses the outcome associated with this method in six patients with seven tumours, particularly with respect to its use in those with phaeochromocytoma.

Clinical details are shown in *Table 1*; all patients were female. Three had non-functioning adrenal tumours, and three had functioning tumours causing hypertension, one as a result of Conn's syndrome with hyperaldosteronism and two as a result of phaeochromocytoma. One patient with multiple endocrine neoplasia had a functioning bilateral tumour that was found by family screening.

Surgical technique

Computed tomography (CT) was performed before surgery so that a horizontal line could be traced on the abdominal wall in the scan section at the site of the adenoma to enable location of the suprarenal gland during the operation.

The patient was placed supine and turned 15° to the left over a pneumatic balloon. The laparoscopic tower was situated at the right of the patient's head, the surgeon to the left and the assistant to the right. A 2·5-cm incision was made 5 cm below the costal margin along the line of the scapula. The muscular layer was incised down to the retroperitoneal space to allow insertion of an index finger for blunt retroperitoneal dissection. A balloon trocar (sheath with a hermetic balloon and transparent tip; Origin, USA) was inserted and inflated to create the retroperitoneal space. After 4–5 min the balloon was deflated and the balloon trocar removed: this was replaced with a Hasson trocar, through which a 10-mm straight telescope (0°) was introduced. Three trocars were inserted; one 10-mm trocar on either side, to act as operating channels, and one 5-mm trocar below the costal margin, along the line of the scapula, for traction and the aspiration or irrigation tube (*Fig. 1*). Gerota's capsule was opened and the superior renal pole identified. The adrenal gland was identified from the preoperative skin marking. The adrenal vein was identified and divided between clips. Small arteries found during dissection were ligated or cauterized. After resection the telescope was changed to a 10-mm port and the

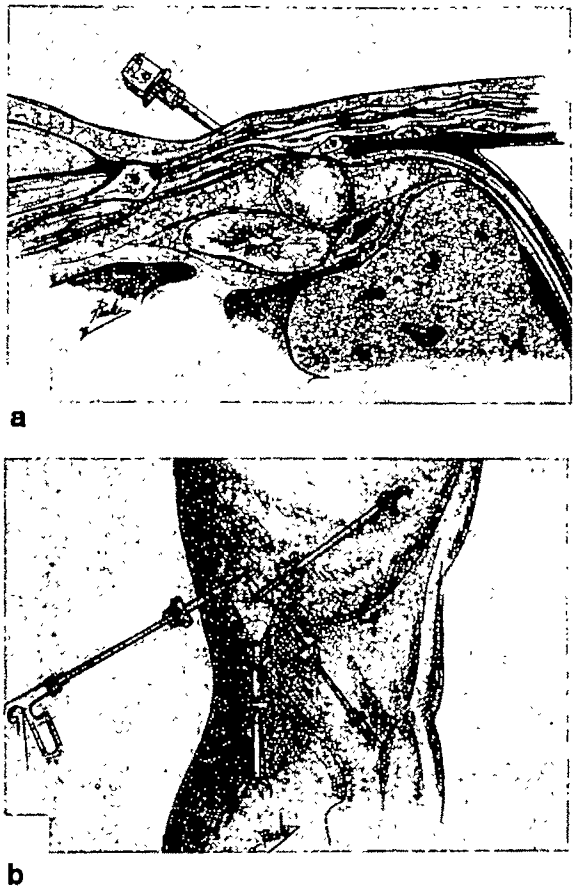

Fig. 1 Method for creating the retroperitoneal space with the trocar balloon

Paper accepted 30 September 1995

Table 1 Patient characteristics

	Patient no.					
	1	2	3	4	5	6
Age (years)	65	17	51	69	57	50
Side	Right	Left	Bilateral	Right	Right	Right
Tumour size (cm)	1·1 × 1·4	8 × 5	Right: 4 × 2 Left: 2 × 2	5 × 3	3 × 3	3 × 4
Histology	Adenoma	Phaeochromocytoma	Right: Phaeochromocytoma Left: Hyperplasia	Adenoma	Adenoma	Adenoma
Duration of operation (min)	150	135	Right: 120 Left: 150	150 (conversion)	100	120
Hospital stay (days)	3	3	5	3	7	3

specimen removed through the initial 2·5-cm incision. Intravenous sodium nitroprusside was used to control any hypertension caused by tumour manipulation.

Results

One patient required conversion to laparotomy because of difficulty creating the retropneumoperitoneum; the remainder were completed endoscopically. The duration of operation ranged from 100 to 150 min (270 min in the patient who had bilateral resection: 120 min right, 150 min left). Blood transfusion was not required. There were no perioperative complications and the duration of hospital stay ranged between 3 and 7 days. Histopathological diagnosis was adenoma (four), phaeochromocytoma (two) and adrenal medullary hyperplasia (one).

Discussion

Endoscopic retroperitoneal dissection, originally designed for inguinal hernia repair has been used to perform adrenalectomy either by finger[5] or balloon dissection[6]. The present method enables dissection through a trocar under visual control. It is quicker than in previous reports of transabdominal laparoscopic adrenalectomy (up to 150 min compared with 150–570 min)[3,4]. Possible dangers including renal vein or vena caval damage and air embolus were not experienced in this series. Hospital stay was less than a week.

Phaeochromocytomas are usually removed anteriorly because the tumour may be located outside the adrenal gland but modern techniques including CT, magnetic resonance imaging and scintigraphy enable accurate preoperative localization. It is conventional to ligate the renal vein early during phaeochromocytoma removal to prevent hypertension, but this may be achieved laparoscopically, and careful intraoperative monitoring and use of hypotensive agents can reduce this problem.

An increasing concern is the small adrenal tumour found incidentally during abdominal imaging. These 'incidentalomas' are frequently treated conservatively but 25–30 per cent may be small phaeochromocytomas. Endoscopic removal may be particularly indicated.

In the present study six of seven adrenal tumours up to a maximum of 8 cm in diameter were successfully removed without complications and the technique deserves further investigation.

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British Journal of Surgery 1996, 83, 989–991

Technetium-99m sestamibi parathyroid localization is accurate enough for scan-directed unilateral neck exploration

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A retrospective study was conducted into technetium-99m sestamibi imaging of primary hyperparathyroidism to determine the accuracy of identification and localization of parathyroid pathology. Of 56 patients studied, 48 had full preoperative scan data, operative data and pathological results analysed. Overall scan accuracy was 96 per cent. For single gland pathology (adenoma) imaging had a sensitivity of 97 per cent, a specificity of 100 per cent and a positive predictive value of 100 per cent. For single gland disease the side was correctly identified in 100 per cent of cases and the site in 94 per cent, but the respective values were only 82 and 79 per cent for multiple gland pathology. Technetium-99m sestamibi imaging is highly sensitive and accurate for primary hyperparathyroidism, with sufficient positive predictive value and accuracy in single gland disease to allow scan-directed unilateral neck exploration.

Successful treatment for hyperparathyroidism requires identification of the abnormal gland(s) and surgical removal. Gland localization is usually done during operation by the surgeon, with the best results and lowest morbidity rates being obtained when the operator is experienced in parathyroid surgery. A variety of techniques (ultrasonography, computed tomography, magnetic resonance and thallium-201 imaging) have been used for preoperative gland localization, but differences in sensitivity of detection have resulted in most parathyroid surgeons not using the techniques before 'first-time' neck exploration.

Recently, combined iodine-123–technetium-99m sestamibi (^{123}I–^{99m}Tc sestamibi) subtraction scanning has been shown to have tissue uptake characteristics suitable for parathyroid imaging with improvements in performance over thallium–technetium-99m pertechnetate subtraction imaging[1]. The accuracy of the scan in single gland disease has raised the issue of whether routine preoperative imaging might permit the extent of neck exploration to be adjusted according to the results.

A retrospective study was conducted into the accuracy of combined ^{123}I–^{99m}Tc sestamibi imaging in predicting the number of involved parathyroid glands and the localization of both single and multiple gland pathology.

Patients and methods

The notes of 56 consecutive patients operated on as a primary procedure for biochemically proven hyperparathyroidism were reviewed. All patients had preoperative ^{123}I–^{99m}Tc sestamibi imaging and were operated on by the same surgeon (R.E.C.C.). The following data were recorded:

1. The written preoperative report on the ^{123}I–^{99m}Tc scan:
   (a) The number of parathyroid glands predicted as abnormal (either one or more than one) or if the scan was reported as inconclusive or normal.
   (b) The predicted side of any abnormal glands identified.
   (c) The predicted site of any abnormal glands identified (recorded as upper pole, lower pole or specific atypical site).
2. The operative findings as recorded on the operation note:
   (a) The number of abnormal glands identified.
   (b) The side of the abnormal gland(s).
   (c) The site of the abnormal gland(s) (upper pole, lower pole or specified atypical site).

Standard operative technique during the study involved a symmetrical skin crease incision allowing full exposure of both thyroid lobes with preoperative methylene blue dye infusion. Exploration was always commenced on the side suggested by the scan in cases of apparent single gland disease. In the first 25 patients all four glands were exposed and biopsies taken even if the peroperative diagnosis was suspected adenoma. In cases where both scan and peroperative diagnosis was of a solitary adenoma, histopathological examination confirmed this in 100 per cent of cases. Subsequently, in patients 26–56, in all of whom the peroperative diagnosis was adenoma, biopsy was either not performed or confined to the ipsilateral macroscopically normal gland.

The histopathological diagnosis was compared with scan results and details of follow-up, including calcium level and parathyroid status, were determined.

Results

Full data were retrieved on 48 patients (86 per cent). The remainder were excluded because of incomplete or absent data due to either the death of the patient (none as a result of parathyroid disease) or loss of the complete operative record. The unit received referrals from the Regional Renal Unit, and eight patients had hyperparathyroidism related to chronic renal failure. The results are shown in *Tables 1* and *2*. The scan diagnosis agreed with operative findings in 96 per cent of cases.

The sensitivity for identification of single gland pathology was 97 per cent, with a specificity of 100 per cent, and a positive predictive value of 100 per cent. No scan predicted single gland disease where there was actually multiple gland pathology. The scan reported as inconclusive was from a patient with chronic renal failure who was found, at operation, to have four moderately hyperplastic glands (confirmed histologically). The normal scan result was confirmed at operation with four macroscopically and histologically normal parathyroid glands. This patient continues to have a raised serum parathyroid hormone level of undiagnosed origin. The erroneous scan was reported as two abnormal glands which at operation were found to be a single parathyroid adenoma and a contralateral thyroid adenoma.

Paper accepted 1 November 1995

Table 1 Detection of pathology: number of abnormal parathyroid glands

	Abnormal glands found at operation	
Scan results	$n = 1$	$n > 1$
Abnormal glands		
$n = 1$	35	0
$n > 1$	1	10

Of the 48 scans, one was inconclusive and one gave a normal result, confirmed at operation. For solitary adenoma detection, scanning had a sensitivity of 97 per cent, a specificity of 100 per cent and a positive predictive value of 100 per cent

Table 2 Scan localization of adenoma when scan predicted only a single gland involved

	No. of patients ($n = 35$)
Side and site* correct	33
Side only correct	2
Site only correct	0
Neither correct	0
Atypical sites detected†	4 of 4

Correct predictive ability of scan for single gland: side, 100 per cent; site, 94 per cent (including 100 per cent of ectopic glands). *Site means location of single gland to upper pole, lower pole or atypical site; †thymus, paraoesophageal, paratracheal, lateral

All other patients remained euparathyroid at long-term follow-up, including those with chronic renal failure. Mean preoperative and postoperative corrected serum calcium levels were significantly different (2·88 (range 2·42–3·56) *versus* 2·30 (range 1·55–3·36) mmol/l respectively, ($P < 0·001$). No reoperations were recorded during the study.

Although scanning was highly accurate in differentiating between single and multiple gland disease, localization of every hyperplastic gland in patients with multiple gland disease was only moderate. In the ten patients with multiple gland disease, the preoperative scan detected only 23 of 28 abnormal glands, with the side of each gland correctly predicted in 23 (82 per cent) of 28, and the sites in 22 (79 per cent) of 28. However, when the predicted number of pathological glands was one, the scan correctly predicted the side of the lesion in all cases and the site in 94 per cent (*Table 2*). In both cases of inaccurate site prediction a prolapsing upper gland was accurately lateralized by the scan before operation in four of four patients.

Discussion

As with other relatively uncommon surgical procedures, it is generally accepted that parathyroid surgery is ideally performed by an experienced parathyroid surgeon. Trained surgeons are highly successful at localizing the site of parathyroid gland pathology in hyperparathyroidism[2], and experience is the most important factor in successful treatment of primary hyperparathyroidism[3]. Previous studies have suggested that imaging should be reserved for re-exploration surgery or difficult diagnostic problems[4]. Previous results of radionuclide imaging of the parathyroids using thallium–technetium pertechnetate subtraction imaging were variable[5], with relatively poor success in predicting multiple gland pathology[6]. Some authors offer only weak support for the accuracy of imaging being sufficient to permit scan-directed unilateral neck dissection[7] and others question the value of imaging in relation to operating time and outcome[8,9]. The advent of ^{123}I–^{99m}Tc sestamibi imaging[10,11] has improved the accuracy of parathyroid localization. Previous small studies have given encouraging results with improved sensitivity for identifying both solitary and multiple gland pathology[12], with up to 88 per cent preoperative sensitivity for identification of a solitary adenoma in one study[13]. The present results indicate that the sensitivity of ^{123}I–^{99m}Tc sestamibi imaging for single gland pathology is better than previously reported results. Overall concordance of scan result and operative findings was 96 per cent in the presence of, and number of, pathological glands. In particular, no case of hyperplasia was diagnosed before operation as a solitary adenoma. This, together with the 100 per cent accurate prediction of the side of the adenoma and 94 per cent accurate localization (including all atypically sited adenomas), adds considerably to the argument that, following preoperative ^{123}I–^{99m}Tc sestamibi imaging unilateral parathyroid exploration may be justified[14].

Although ^{123}I–^{99m}Tc sestamibi imaging is not accurate in localizing every pathological parathyroid gland, it provides accurate preoperative identification of patients with a solitary adenoma. It is sufficiently reliable in the prediction of side and site of a solitary adenoma that unilateral neck exploration may safely be offered to patients on the basis of a preoperative scan.

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British Journal of Surgery 1996, 83, 992–993

For debate

Conservative management of fibroadenoma of the breast

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Management of fibroadenoma of the breast has become a subject for debate. Before experience with cytological techniques, breast lumps were routinely excised, allowing diagnosis and management of fibroadenoma at one procedure. More recently, several groups have investigated non-operative management of selected fibroadenomas after a benign clinical, radiological and cytological diagnosis[1–3]. The natural history of fibroadenoma is considered here, to determine potential problems in patient selection and follow-up for a conservative management regimen.

Although fibroadenoma may develop at any stage of reproductive life, it is predominantly a disease of young women, with a peak incidence in the 21–25 years age group and a median age at diagnosis of about 30 years[4,5]. Fibroadenoma is considered to be an aberration of normal lobular development and may contain stromal and epithelial lobular components in various patterns. The exact aetiology is unclear, but studies of plasma reproductive hormone levels and hormone receptor prevalence suggest the influence of hormonal factors on the developing terminal duct lobular unit[6,7].

During its growth phase, a fibroadenoma may double in size every 6–12 months. Recent studies using ultrasonography confirm clinical findings that a proportion may regress, while growth in some may continue unrestrained, with the development of giant lesions[8]. Generally, however, growth is self-limiting over several years and most stabilize at a size of 1–3 cm. Previously stable lumps may enlarge during pregnancy or other periods of hormonal flux[1–5]. Infarction may occur, leading to calcification and the pathognomonic macroscopic 'popcorn' calcifications seen in mammograms.

The classical features of a discrete, smooth, mobile and rubbery lump are commonly seen in patients under the age of 25 years. Cytological diagnosis of fibroadenoma has an estimated sensitivity of 87 per cent and specificity of 76 per cent in experienced hands[7]. There is a false-negative rate for cancer of 1–2 per cent in patients over 35 years of age[1]. Combined clinical and cytological diagnosis of fibroadenoma in a prospective study of 92 patients aged less than 35 years was accurate in only 56 of 77 lesions, but the false-negative rate for cancer was zero[9].

Although fibroadenoma is not generally considered to be premalignant, more than 100 cases of malignant transformation within a fibroadenoma have been reported, with an estimated incidence of 0·12–0·3 per cent[6]. Malignancy includes sarcoma and carcinoma, of both *in situ* and invasive varieties, with a lobular pattern being the most common. Recent data also suggest that a fibroadenoma with complex histology may indicate increased risk of cancer in the rest of the breast parenchyma, particularly in patients with a positive family history[10]. Malignancy in fibroadenomas is typically found in patients one to two decades older than those with benign pathology[6]. Growth of the lump is the most common presenting symptom of malignant transformation, although tumour size itself is not related to the likelihood of malignancy. The malignant element is often discovered on pathological examination of a clinically benign lump. Localized pain or extramammary symptoms have rarely prompted presentation to medical attention[6].

Several workers have described the selection of patients who can safely be offered non-operative management of fibroadenoma. Cant *et al.*[2] recommended a conservative approach in women under 25 years of age with clinically and cytologically benign fibroadenoma. Wilkinson and colleagues[9] extended this age limit to 35 years. There was no case of a missed diagnosis of malignancy in the fibroadenoma in either series, although, perhaps in the light of findings from Dupont *et al.*[10], diagnosis of a complex histology is as important on pathological examination as exclusion of malignancy. There are currently no published data on the relationship between the pattern of cytology in fibroadenoma and later risk of breast cancer.

The primary aim in follow-up of conservatively managed fibroadenoma must be early detection of malignancy. The problem for the clinician is that, aside from age at diagnosis, initial malignant symptoms significantly overlap the natural history of the benign lesion. Mammography is insensitive in the early detection of malignancy within a fibroadenoma, probably because the radiodensity and macrocalcification commonly seen in the benign lesion may mask early radiological signs. Once the false capsule has been breached by invasive tumour mammographic signs are more apparent, but this may be relatively late in the disease process. Reliable sonographic changes of early malignancy are as yet incompletely defined[7–9].

Hindle *et al.*[3] recommended 'regular breast examinations and mammography', although the rationale behind this approach, and the frequency and duration of its adoption, were not discussed. Patients enrolled in the study by Wilkinson and colleagues[1,9] were reviewed four times in 12 months, after which the fibroadenomas were excised. A prospective protocol for patients offered conservative therapy outside a trial was not discussed[1,9] and, although Dent and Cant[7] emphasized the need for careful follow-up of conservatively managed patients, no regimen was detailed.

As well as medical considerations, psychological factors are important. If a patient is told that the tumour is benign she may ignore signs suggestive of malignancy. By contrast, if she fully understands that malignant transformation, although unlikely, is not impossible, she may find the presence of the lump intolerable and prefer to have it removed. Recent trials of conservative management have found that up to 90 per cent of women, for a variety of reasons, wish to have the lump excised[7,9].

Paper accepted 6 September 1995

The ideal management of fibroadenoma requires further consideration. Although conservative therapy is not an unrealistic aim, surgical removal should not be considered a radical approach, particularly in patients with a family history of breast cancer. Excision has the attractions of minimal morbidity, complete pathological examination, high patient acceptability and 100 per cent cure. For those who favour it, the aims and risks of non-operative therapy need to be clarified, with the issues of effective screening for malignant transformation, patient compliance and overall cost considered before adoption of this approach.

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British Journal of Surgery 1996, 83, 994–996

Breast conservation or mastectomy: treatment choice of women aged 70 years and older

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Fifty women aged 70 years and older with newly diagnosed carcinoma of the breast were prospectively studied after being offered a choice of four treatment options. Thirty-four of 38 patients who chose their own treatment had breast conservation; four opted for mastectomy. At 12-month follow-up only two women were unhappy with their choice of treatment. It is concluded that elderly women should be involved in deciding the treatment of their breast cancer.

More than one-third of women treated for breast cancer in the UK are over 70 years of age[1]. It is commonly considered that women older than 70 years accept mastectomy more readily than younger women, and that radiotherapy is poorly tolerated in this age group[2]. Earlier reports that tamoxifen alone may be adequate treatment in all elderly patients are now discredited[1,3] and mastectomy is usually advised. The aims of this study were to involve elderly women in decisions about their treatment, ensure that they were informed about the options available and avoid suboptimal treatment.

Patients and methods

All women aged 70 years and older who presented between 1989 and 1992 with a new diagnosis of breast cancer were reviewed. The diagnosis was made by a combination of history, examination, fine-needle aspiration cytology and mammography. Most women were accompanied by a relative during the initial outpatient consultation and once a diagnosis of breast cancer had been made the treatment options available to the patient were discussed. The four treatments offered were: tamoxifen alone; complete local excision and tamoxifen; modified radical mastectomy and tamoxifen; and complete local excision, radiotherapy and tamoxifen. Complete local excision was an entire macroscopic clearance of the tumour. Radiotherapy consisted of 50 Gy to the breast, 25 Gy to the axilla and supraclavicular fossa, and a 15-Gy boost to the tumour bed.

After discussing the options in detail, including advantages and disadvantages, patients were encouraged to ask questions, which often included asking the surgeon his/her preference. However, if patients did not ask this they were not told. The patient was then given an information sheet to take away which reiterated the choices available, the advantages and disadvantages of each choice, the approximate risk of recurrence with each treatment and the likelihood of requiring further intervention. After the initial consultation with the surgeon, the patient was seen a few days later by the breast-care sister and the same treatment options were discussed again. At the end of this discussion the patient selected treatment if she wished to do so. There was no coercion to select a specific treatment and patients were at liberty to say that they wished the surgeon to make the choice. After the chosen treatment the women were reinterviewed by the breast-care sister 6 and 12 months after the initial clinic visit. Thus the '6-month' interview typically took place about 3 months after completion of radiotherapy. A standard questionnaire was completed at interview, recording side-effects experienced by the patient, whether the patient considered that her treatment choice was correct, and assessment by the patient and nurse of the cosmetic outcome in women who had breast-conserving treatment. Patients were asked to score the cosmetic result of their surgery on a scale of 1–5 (1, very happy; 5, very unhappy); the breast-care nurse independently scored the cosmetic result on the same scale. Side-effects of radiotherapy were categorized as minor, moderate or severe (*Table 1*). The patients were also examined in the follow-up clinic at these times for signs of local recurrence or metastatic disease. The cause of death for patients who died during the study was ascertained from the death certificate or hospital notes.

Results

Age of patients in this study is shown in *Fig. 1*. The size and grade of the tumours are given in *Table 2*. Thirty-

Table 1 Incidence of side-effects associated with radiotherapy*

Severity of side-effect	No. of patients
Nil	1
Minor	28
Moderate	4
Severe	3

*Minor (side-effects include tiredness and skin reddening); moderate (breast shrinkage and asymmetry); and severe (skin breakdown and pulmonary fibrosis)

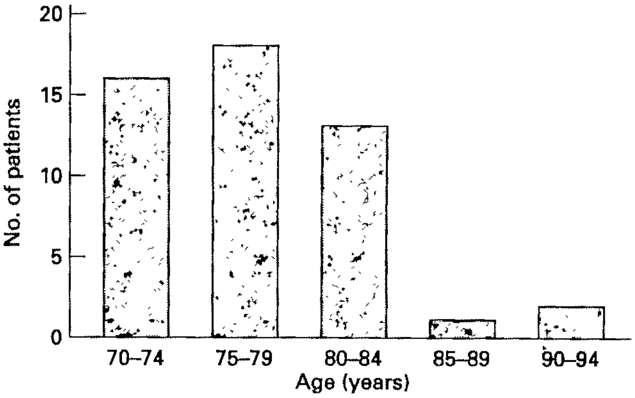

Fig. 1 Age of 50 patients with carcinoma of the breast at enrolment

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Presented to the British Association of Surgical Oncology, in Rhyl, UK, June 1993
Paper accepted 4 August 1995

Table 2 Tumour size and grade

	No.
Grade	
I	10
II	22
III	18
Total	50
Size (mm)	
Less than 9	0
10–19	21
20–29	18
30–39	7
40–49	2
More than 50	2
Total	50

Table 3 Treatment chosen by patients

Treatment	No. of patients
Tamoxifen	1
Complete local excision and tamoxifen	2
Mastectomy and tamoxifen	4
Complete local excision, radiotherapy and tamoxifen	31

Table 4 Treatment chosen by surgeon

Treatment	No. of patients
Tamoxifen	2
Complete local excision and tamoxifen	5
Mastectomy and tamoxifen	0
Complete local excision, radiotherapy and tamoxifen	4
Radiotherapy	1

eight of the 50 patients in the study chose their treatment (*Table 3*). The remainder elected to let the surgeon decide (*Table 4*). Four patients chose mastectomy. Three said that they had chosen it because the surgeon had told them that he thought it was the most appropriate, and the fourth patient, although suitable for breast-conserving treatment, decided that radiotherapy was 'too much trouble'. Twelve patients died during the study; five from distant spread of the cancer and seven from causes unrelated to cancer. The median duration of follow-up was 21 months. There were no local recurrences. One patient developed a contralateral breast cancer, having had the initial tumour treated by complete local excision, radiotherapy and tamoxifen. The contralateral tumour was treated similarly but the patient died 26 months after development of the second tumour. All patients who underwent breast-conserving treatment were either very happy or happy with the cosmetic result (score 1 or 2) at 6 and 12 months. Tolerance to radiotherapy was generally good; the side-effects experienced are given in *Table 1*. All patients completed their course of radiotherapy. All but two of the patients who chose their treatment considered that they had made the right choice. The two unhappy patients were worried by the initial skin reddening following radiotherapy.

Discussion

A previous study of patient choice in breast cancer treatment showed a preference for mastectomy, but considered women only below the age of 65 years[4]. Elderly women have been excluded from many of the large studies of breast-conserving treatment for breast carcinoma.

One factor influencing the choice of treatment for a patient is the desire to avoid therapies associated with morbidity that outweighs their benefit. Side-effects considered tolerable in a younger patient may not be so in an elderly patient, and a belief that adjuvant radiotherapy causes excessive morbidity in the elderly may be one reason why the treatment of elderly patients varies widely from that regarded as optimal. In fact, there is evidence that elderly people tolerate radiotherapy to the breast as well as younger people[5]; the results of this study on the side-effects of such treatment support this conclusion.

Breast-conserving treatment using tamoxifen alone, tamoxifen with local excision of the tumour, or local surgical excision alone would be considered inadequate local treatment in young women. There is good evidence that breast cancer in the elderly is as aggressive a disease as it is in young women, regardless of whether aggression is measured by tumour grade[6] or nodal involvement[7]. In addition, when allowance is made for other causes of death, there is little difference in 5-year survival rates between younger and elderly patients with breast carcinoma[8]. If tamoxifen alone is used to treat elderly patients then less than 50 per cent will have their disease controlled locally in the long term and a smaller proportion will have a complete remission[9]. Patients who experience relapse will usually require operation to control local disease when they are inevitably older, and possibly less fit, than if they had been operated on at the time of the original diagnosis. While women who have a complete response to tamoxifen have very good 5-year survival, clinical prediction of response is inaccurate unless immunocytochemical assay of fine-needle aspirates is used to assess oestrogen receptor status[10]. The use of local excisional surgery alone will also result in high local recurrence rates[9]. Tamoxifen with local excisional surgery will improve local disease control but not to the same extent as adjuvant radiotherapy. Modified radical mastectomy controls local disease and is well tolerated by elderly patients[11]. It is appropriate therefore to offer elderly women with breast cancer the same treatment as younger women.

Nowadays, younger women are well informed from reading the lay press and magazines about the treatment options for breast cancer and in particular about the alternatives to mastectomy. Despite this information, patients may be strongly influenced by the advice of their surgeon and this may explain the wide differences in the published studies of women's choice between mastectomy and breast conservation[4,11,12]. In contrast, older women have grown up in an era in which mastectomy was the accepted treatment for breast cancer, and they may consent to this treatment more readily than younger women. This does not imply that they would not prefer breast-conserving treatment. The present study demonstrates that elderly women prefer breast conservation even if this involves the considerable inconvenience of travelling to a distant centre to receive radiotherapy.

It is suggested that women aged 70 years and older with breast cancer should be treated in the same way as younger women.

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British Journal of Surgery 1996, 83, 997–1001

Factors affecting outcome of patients with impalpable breast cancer detected by breast screening

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Factors affecting completeness of excision and outcome, whether conservation or mastectomy, in 152 patients with localized impalpable breast cancer undergoing therapeutic needle-guided wide local excision were assessed by univariate and multivariate analyses using multiple logistic regression. Independent factors related to completeness of excision at the first operation were operator experience ($P = 0.0001$), and size of the lesion ($P = 0.005$). Factors related to outcome were operator experience ($P = 0.0003$), more experienced operators having a higher rate of breast conservation, and tumour size ($P = 0.0001$), larger lesions being more likely to be treated by mastectomy. Patients initially operated on by the two most experienced surgeons were more than four times less likely to undergo mastectomy than those whose initial wide local excision was performed by a less experienced surgeon.

Excision biopsy for impalpable breast cancer results in up to 60 per cent of patients having an incomplete excision[1,2]. It is now possible, with the use of stereotactic and ultrasonographically guided fine-needle aspiration cytology, to identify the majority of patients with impalpable malignant lesions before operation[3] and permit the first surgical procedure to be therapeutic. It is the policy in the authors' unit to perform a therapeutic needle-guided wide local excision for patients with localized impalpable lesions (4 cm or less) from which malignant cytology has been obtained[4]. If the initial excision is incomplete then patients are selected for either re-excision or mastectomy[5]. The aims of this study were to determine which factors affect the completeness of excision at initial operation and which influence whether the patient is ultimately treated by breast-conserving therapy or mastectomy.

Patients and methods

A total of 152 patients with localized (4 cm or less on mammography) screen-detected impalpable breast tumours diagnosed by stereotactic or ultrasonographically guided fine-needle aspiration cytology underwent a therapeutic wide local excision between 1 January 1991 and 30 June 1993. The notes of these patients were reviewed and data extracted on the factors listed in *Table 1*. These factors were then correlated with the outcome of surgery.

Patients were defined as having had a complete excision if the mammographic lesion had been completely excised and all resection margins were 1 mm or more clear of invasive and *in situ* disease on histological assessment.

Table 1 Factors studied

Nature of mammographic lesion
  Presence of microcalcification
  Type of microcalcification (branched or non-branched)
  Presence of mass lesion
  Distortion of architecture
  Combination of these features
Operator
  Experience (log of number of operations performed during the study)
  Experience (more than 20 operations) *versus* no experience (less than 15 operations) during the study
Method of localization
  Ultrasonography *versus* stereotactic
Pathological features
  Size of lesion (cm)
  Volume of excision
  Invasive cancer or *in situ* disease
  Type of invasive or *in situ* cancer
  Presence of extensive *in situ* component within invasive cancer
  Histological axillary node involvement

Surgeons

Two surgeons performed almost 70 per cent of the operations and these have been designated as experienced operators (*Table 2*). One was a consultant and the other a senior registrar with a specific interest in breast disease who had been attached to the unit three times for a total of 3·5 years. In contrast, six of the seven inexperienced surgeons were attached to the unit for short periods of training. During their attachment to the breast unit, senior registrars and registrars were trained to perform wire localization biopsy in patients undergoing diagnostic excision. Thereafter, they were supervised during the first three wire-guided therapeutic wide local excisions for cancer and were then allowed to perform these procedures with no consultant present at the operating table, but available in the theatre suite.

Operative procedure

All patients underwent wire-guided local excision. This was performed using stereotactic guidance in 121 patients and ultrasonographic guidance in 31. After removal of the specimen it was orientated with ligaclips and orientated specimen radiography was performed in an attempt to achieve complete excision at one operation as previously described[4]. The external surfaces of the specimen were painted with ink and the specimen placed on a trimming jig with the anterior surface uppermost. Serial slices (4 mm thick) were taken in a plane parallel to the chest wall and subjected to radiography. The appropriate areas

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Paper accepted 7 September 1995

Table 2 Operators*

	No. of surgeons	Total no. of operations	Percentage of all operations	Grade of surgeon: Consultant	Grade of surgeon: Senior registrar	Grade of surgeon: Registrar
Experienced	2	106	71	1	1	—
Inexperienced	7	46	29	1	4	2

*Experienced surgeons performed more than 20 operations during the study period while inexperienced surgeons carried out less than 15

were blocked to include all six possible resection margins and all areas of radiological abnormality.

Protocol

A standard policy for re-excision and mastectomy was employed throughout the study period (*Table 3*).

Statistical analysis

Univariate analysis using logistic regression, χ^2 and Fisher's exact tests and multivariate analysis using multiple logistic regression were used to relate the factors in *Table 1* with completeness of excision at the first operation and outcome (breast conservation or mastectomy). Analyses were performed for the whole group (both invasive and *in situ* disease) and for the groups of patients with invasive and *in situ* disease separately.

Table 3 Unit protocol for re-excision and mastectomy

- Re-excision
  - One (focal) margin involvement and tumour either DCIS or invasive cancer and EIC-negative
- Mastectomy
  - Focal margin involvement and invasive cancer and EIC-positive
  - More than one margin involved
  - Margin involvement but impossible to determine extent or location of residual disease
  - Multifocal invasive cancer
  - DCIS more than 4 cm irrespective of margin involvement

DCIS, ductal carcinoma *in situ*; EIC, extensive *in situ* component

Results

Some 100 patients had invasive cancer and 52 *in situ* disease. The pathological size of the lesions ranged from 0·3 to 5 cm. Twelve patients had invasive tubular cancer and 22 of 100 with invasive cancer had an extensive *in situ* component. The volumes of excision ranged from 13 to 240 ml and seven of the 132 patients who had axillary nodes excised had involved axillary nodes.

A total of 122 lesions (80 per cent) were completely excised at the first operation, including five patients with ductal carcinoma *in situ* (DCIS) extending over a distance of more than 4 cm and two with multifocal disease. According to the protocol in *Table 3* these latter seven patients underwent mastectomy. Some 126 patients (83 per cent) were treated ultimately by conservation therapy and this included 115 who had an adequate excision at the first operation and 11 who underwent successful re-excision. Twenty-six patients (17 per cent) were treated by mastectomy.

Univariate analysis: all cancers

Of factors influencing the likelihood of complete excision and surgical outcome, operator experience and lesion size were significant in univariate analysis (*Tables 4* and *5*). The frequency of complete excision for each individual surgeon related to the number of operations carried out by that surgeon during the study is shown in *Fig. 1*. One of the inexperienced surgeons was a consultant who performed only a few procedures (*Table 2*). During their first operations the six inexperienced surgeons who were not consultants were supervised and 11 of these 18 excisions had clear histological margins compared with nine of 28 in later operations which were unsupervised. This difference was not statistically significant. A major

Table 4 Significant factors related to margin involvement in univariate analysis

	No. of patients	Excision (%): Complete	Excision (%): Incomplete	*P*
Surgeon				
Experienced	106	102 (96)	4 (4)	0·0001
Inexperienced	46	20 (43)	26 (57)	
Microcalcification				
Yes	80	59 (74)	21 (26)	0·037
No	72	63 (88)	9 (12)	
Mass				
Yes	64	57 (89)	7 (11)	0·024
No	88	65 (74)	23 (26)	
EIC†				
Yes	22	15 (68)	7 (32)	0·022
No	78	69 (88)	9 (12)	
Mean(s.e.m.) size (cm)	—	1·40(0·09)	2·17(0·22)	0·0001

Values in parentheses are percentages. †Invasive cancers only. EIC, extensive *in situ* component

Table 5 Significant factors related to surgical outcome in univariate analysis*

	No. of operations	Breast conservation (%): One excision	Breast conservation (%): Re-excision	Mastectomy	*P*
Surgeon					
Experienced	106	96 (91)	1 (1)	9 (8)	0·0002
Inexperienced	46	19 (41)	10 (22)	17 (37)	
Mass					
Yes	88	59 (67)	9 (10)	20 (23)	0·031
No	64	56 (88)	2 (3)	6 (9)	
Invasive					
Yes	100	81 (81)	6 (6)	13 (13)	0·062
In situ					
Yes	52	34 (65)	5 (10)	13 (25)	

Values in parentheses are percentages. *Size also significant see *Table 6*

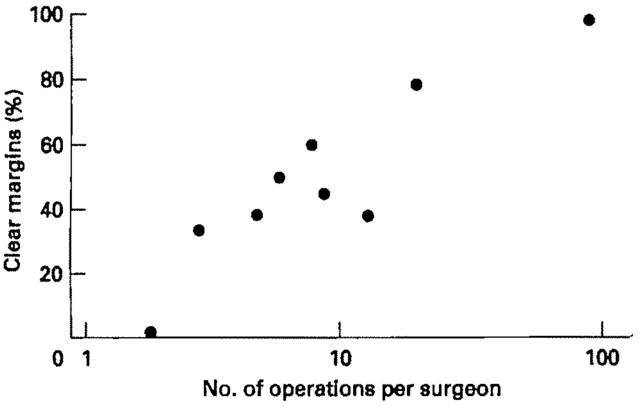

Fig. 1 Lesions completely excised compared with experience (plotted as the number of operations performed during the study – log scale)

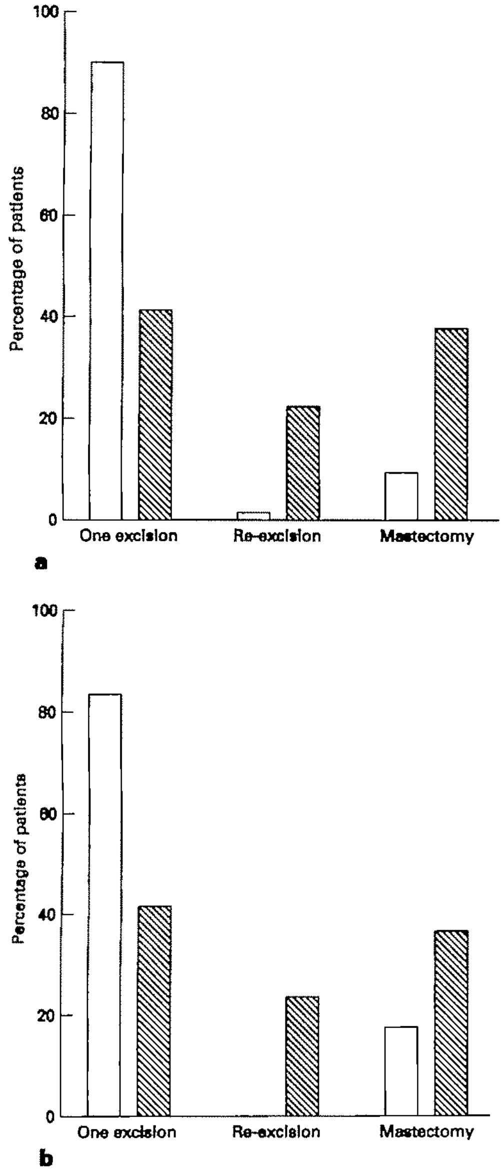

Fig. 2 Outcome in patients for a all cancers and b *in situ* cancers related to whether their initial operation was performed by an experienced (□) or inexperienced (▨) surgeon

problem during unsupervised operations was removal of areas of microcalcification in more than one piece, which made assessment of completeness of excision difficult. The three possible outcomes, namely complete excision at one operation, re-excision and mastectomy, according to whether the initial operation was performed by an 'experienced' or 'inexperienced' surgeon are given in *Fig. 2*. Patients who had their initial operation performed by an 'inexperienced' surgeon were greater than four times more likely to require a mastectomy than those whose initial operation was undertaken by a more experienced surgeon. The size of the lesion related to outcome is presented in *Table 6*: the mean size of the lesion increased as the extent of local surgery increased. The 12 patients with tubular cancer had a complete excision at the first operation but this was not significantly different from the rate of excision in those with invasive cancer of no special type.

Table 6 All cancers: size of lesion related to outcome

Outcome	No. of patients	Mean(s.e.m.) size (cm)
Single excision	115	1·25(0·06)
Re-excision	11	1·86(0·33)
Mastectomy	26	2·74(0·29)

Multivariate analysis: all cancer

Margins. The two factors retaining independent significance for completeness of excision were operator experience ($P = 0·0001$), more experienced operators achieving a higher rate of complete excision, and size of lesion ($P = 0·005$), larger tumours being less likely to be completely excised (*Table 7*).

Outcome. Factors related to outcome were operator experience ($P = 0·0003$) and tumour size ($P = 0·0001$). Patients were less likely to be treated by mastectomy if their initial operation was performed by a more experienced surgeon and larger tumours were more likely to be treated by mastectomy (*Table 7*). There were no significant relationships between other factors and outcome.

Invasive cancer

In multivariate analysis only operator experience ($P = 0·005$) was related to completeness of excision (*Table 7*). Both operator experience ($P = 0·006$) and tumour size ($P = 0·028$) were identified as significant factors related to whether patients had breast conservation or mastectomy.

In situ *cancer*

Lesion extent and operator experience were the only independent significant factors predicting completeness of excision and outcome (*Table 7*). Experienced surgeons were more than twice as likely to excise an *in situ* tumour completely at one operation than less experienced surgeons (*Fig. 2*). The mean size of *in situ* lesions requiring mastectomy was over 3·5 cm (*Table 8*).

Table 7 Regression coefficients estimated by multivariate analysis

	Margins	Outcome
All cancer		
Operator experience	1·51(0·29)	0·98(0·24)
Tumour size	−0·74(0·26)	−1·42(0·32)
Invasive cancer		
Operator experience	1·25(0·33)	0·81(0·30)
Tumour size	−0·57(0·42)	−0·99(0·46)
In-situ cancer		
Operator experience	2·01(0·63)	1·17(0·49)
Tumour size	−1·22(0·49)	−1·87(0·61)

Values in parentheses are s.e.m.

Table 8 *In situ* cancer: size of lesion related to outcome

Outcome	No. of patients	Mean(s.e.m.) size (cm)
Single excision	34	1·53(0·15)
Re-excision	5	2·30(0·66)
Mastectomy	13	3·56(0·33)

Table 9 Reasons for mastectomy

Reason	No. of patients	Residual disease in mastectomy specimen
Invasive cancer		
Multifocal disease	3	0 of 3
Focal margin involvement and EIC-positive	3	1 of 3
Widespread margin involvement	2	1 of 2
Uncertainty about completeness of excision	5	3 of 5
In situ		
Extensive margin involvement	4	2 of 4
More than 4 cm margins clear	5	3 of 5
Uncertainty about completeness of excision	4	3 of 4
Total	26	13 of 26

EIC, extensive *in situ* component

Reasons for mastectomy

Seven patients underwent mastectomy after an apparently complete initial wide local excision because of DCIS extending over a distance of greater than 4 cm (five patients) or because of multifocal invasive cancer (two). The reasons for the remaining 19 patients having a mastectomy are outlined in *Table 9*. Of the 26 patients who underwent mastectomy, 13 were identified as having residual disease in the excised breast after mastectomy. Nine patients underwent mastectomy because of uncertainty over completeness of excision; all had their operations performed by unsupervised, 'inexperienced' surgeons. The finding of residual disease in six of nine of these patients justified mastectomy.

Discussion

The main role of screening is to reduce death from breast disease, but a secondary aim is to reduce morbidity. One way of achieving this is to treat more patients with breast cancer by breast-preserving surgery. Morbidity can also be reduced by identifying those patients with breast cancer before operation to permit the surgeon to perform a therapeutic excision as a first surgical procedure[4]. This study investigated those factors in patients with apparently localized impalpable breast cancer which affect whether the surgeon achieves a complete excision at initial operation and which influence whether patients are ultimately treated by breast conservation or mastectomy. The extent of the lesion was a major factor in determining the surgeon's ability to excise the lesion completely at the first operation. Disease extent also correlated with surgical outcome, with larger lesions being much more likely to require mastectomy.

The other major factor influencing completeness of excision and surgical outcome was experience of the surgeon who performed the initial wide local excision. Experienced surgeons were more than twice as likely to excise an impalpable tumour completely at one operation and patients whose initial operation was performed by an experienced surgeon were more than four times *less* likely to be eventually treated by mastectomy. The majority of inexperienced surgeons were those in training. They were trained according to an agreed protocol and were allowed to perform excision of impalpable tumours only when they were deemed to be competent. An adequate complete excision rate was achieved during the first few excisions when the trainees were supervised. When they started to perform operations alone, however, the rate of complete excision declined because they frequently removed the mammographic lesion in several pieces which made assessment of completeness of excision and the site of any residual disease difficult. In such cases, the authors' protocol dictated that these patients should be treated with mastectomy; a policy that seems justified by the high rate of residual disease in the subsequent mastectomy specimens.

It was also policy to perform a mastectomy for areas of carcinoma *in situ* extending over 4 cm. As all mammographic lesions measured less than 4 cm, a pathological size of more than 4 cm indicated that the histological extent of disease was greater than the mammographic lesion and thus that in these patients was not a reliable marker of the extent of disease. The policy of advising mastectomy for these lesions is based on data from analysis of whole breast specimens[6]. The fact that residual disease was identified in three of five mastectomies performed on patients with DCIS over 4 cm which had apparently been completely excised justifies this policy and suggests that it would not be prudent to include DCIS lesions over 4 cm in size in the current UK randomized study of treatment of DCIS.

The presence of multifocal disease is usually considered an indication for mastectomy[7]. In the present series none of the patients with multifocal disease had residual disease in the removed breast. This suggests that breast conservation therapy may be appropriate in patients with localized multifocal disease[8]. The presence of an extensive *in situ* component (EIC) within an invasive cancer is a risk factor for residual disease in the breast after wide excision[9]. In the present series patients with invasive cancer which was EIC positive were significantly less likely to have an initial complete excision than those with tumours which were EIC negative ($P = 0{\cdot}022$, *Table 4*). However, only one of three patients who had focal margin involvement and an EIC-positive tumour had residual disease in the breast at mastectomy but the numbers are too small to draw any firm conclusions.

The findings of the present study have important implications for the training of surgeons in the removal of screen-detected impalpable tumours. The aim during the study period was to train all senior registrars, and some registrars, attached to the breast unit to remove impalpable breast tumours safely. They started by performing wire localization biopsy under supervision in patients undergoing diagnostic excision. After performing three or four biopsy procedures they proceeded to supervise wire-guided therapeutic excision for breast cancer. When considered to be competent, they were permitted to perform these procedures without an experienced surgeon supervising the operation. This study demonstrates that there is a long learning curve to this procedure and that it is not until a trainee has performed 10–15 of these operations that he/she becomes competent.

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British Journal of Surgery 1996, 83, 1002–1006

Reduced hepatic acute-phase response after simultaneous resection for gastrointestinal cancer with synchronous liver metastases

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Serum cytokines and hepatic acute-phase responses were studied in seven patients undergoing simultaneous resection of primary gastrointestinal cancer and synchronous metastatic liver tumours and in 12 undergoing partial hepatectomy alone for metachronous hepatic metastases. The incidence of postoperative infectious complications was significantly higher after simultaneous resection than after partial hepatectomy alone ($P<0{\cdot}05$). Although the peak interleukin 6 level was significantly higher after simultaneous resection ($P<0{\cdot}05$), plasma levels of acute-phase proteins were significantly lower ($P<0{\cdot}05$). The results suggest that simultaneous resections further reduce the hepatic acute-phase response and render patients liable to infection compared with partial hepatectomy alone, and result in a higher incidence of postoperative infective complications.

The risks associated with simultaneous resection of the bowel and liver for gastrointestinal cancer with synchronous liver metastases have not been clearly determined[1–4]. The hepatic acute-phase response is one of the liver-related host defence mechanisms[5,6] and the hepatic capacity for acute-phase protein synthesis is reduced by partial hepatectomy[7]. Simultaneous resection of liver and bowel may further reduce the hepatic acute-phase response[8]. Simultaneous resection may also increase the production of inflammatory cytokines[5], which are implicated in the pathogenesis of septic complications[9,10].

The aim of this study was to determine the changes in hepatic acute-phase response following simultaneous resection of the liver and bowel, and to identify the operative risk of this procedure.

Patients and methods

Primary and secondary tumours were simultaneously resected in seven patients with hepatic metastases (from colorectal cancer in five patients and from gastric cancer in two), and a further 12 underwent partial hepatectomy alone for metachronous hepatic metastases (from colorectal cancer in 11 and from gastric cancer in one). Indications for the type of liver resection were determined mainly by the size and extent of tumours (*Table 1*). All patients underwent standard liver function testing before surgery. The time sequence changes in serum levels of interleukin (IL) 6, α_1-antitrypsin (AAT), α_1-acid glycoprotein (AAG), haptoglobin and plasma fibrinogen were measured. Peripheral venous blood samples were collected before surgery and on days 1, 3, 5, 7 and 14 after surgery.

The protocol was approved by the hospital ethical committee and all patients gave oral consent before the study commenced.

Serum IL-6 concentrations were determined with a two-step enzyme-linked immunosorbent assay kit (Toray Fuji Bionics, Tokyo, Japan). Plasma fibrinogen level was measured in an autoanalyser (Sankyo, Tokyo, Japan). The serum levels of the other three acute-phase proteins were determined by immunological nephelometry using commercially available antibodies (Hoechst Japan, Tokyo, Japan). The plasma concentrations of these acute-phase proteins were expressed as a percentage of the preoperative value.

The ratio of acute-phase proteins to IL-6 was calculated as the ratio of maximum plasma level of IL-6 after operation.

Statistical analysis of the results was performed with Student's *t* test, Fisher's exact probability method, simple regression analysis, analysis of variance (ANOVA) and Fisher's protected least significant difference (PLSD). Results are presented as mean(s.d.). $P<0{\cdot}05$ was considered statistically significant.

Results

There were no significant differences in age, sex ratio, standard liver function test results and operative parameters between the two groups (*Table 2*). Postoperative complications are shown in *Table 1*. There were no operative deaths in the study. The incidence of postoperative infective complications was significantly higher after the simultaneous resection than after partial hepatectomy alone (43 *versus* 0 per cent, $P=0{\cdot}04$) (*Table 2*).

There was no difference in preoperative serum IL-6 levels between the two groups. All patients showed a striking increase in serum IL-6 concentration on the first postoperative day. The mean(s.d.) peak level of serum IL-6 was significantly higher in patients having simultaneous resection than in those undergoing partial hepatectomy alone (241(181) *versus* 78(29) pg/ml, $P<0{\cdot}05$) (*Fig. 1*). In all patients, blood loss and operating time did not correlate with serum IL-6 level. Serum IL-6 level was significantly higher in three patients who had infective complications than in those who underwent simultaneous resection or partial hepatectomy alone without infectious complications (311(184) *versus* 160(136) *versus* 78(29) pg/ml, $P<0{\cdot}05$, ANOVA and Fisher's PLSD). In patients having simultaneous resection the maximum level of serum IL-6 was no different in patients undergoing gastric resection and in those having colorectal resection.

There were no significant differences between the two groups in terms of preoperative plasma levels of four acute-phase proteins. In all patients plasma levels of these proteins fell significantly on the first postoperative day

Paper accepted 31 October 1995

Table 1 Clinical and operative details of all patients

Patient no.	Age (years)	Sex	Primary site	Type of resection	Postoperative complications
Synchronous metastasis					
1	72	F	Colonic cancer	Right lobectomy and right hemicolectomy	
2	67	M	Rectal cancer	Left lobectomy and abdominoperineal resection	
3	69	F	Gastric cancer	Right lobectomy and distal gastrectomy	Pneumonia
4	67	M	Colonic cancer	Extended right lobectomy and right hemicolectomy	Ascites (not infected)
5	73	F	Gastric cancer	Extended left lobectomy and distal gastrectomy	Pneumonia
6	70	F	Colonic cancer	Left lobectomy and right hemicolectomy	Intraperitoneal abscess
7	55	M	Colonic cancer	Right lobectomy and right hemicolectomy	
Metachronous metastasis					
1	46	F	Colonic cancer	Right lobectomy	
2	76	F	Colonic cancer	Right lobectomy	Deep vein thrombosis
3	72	M	Colonic cancer	Right lobectomy	
4	70	M	Colonic cancer	Right lobectomy	
5	75	F	Colonic cancer	Right lobectomy	
6	73	M	Rectal cancer	Extended right lobectomy	
7	80	M	Gastric cancer	Extended left lobectomy	
8	74	F	Colonic cancer	Extended right lobectomy	
9	42	M	Colonic cancer	Extended right lobectomy	
10	69	M	Colonic cancer	Right lobectomy	
11	48	M	Colonic cancer	Right lobectomy	
12	58	M	Colonic cancer	Extended right lobectomy	

Table 2 Patient details and postoperative morbidity rate

	Synchronous metastases ($n=7$)	Metachronous metastases ($n=12$)	P
Age (years)*	67·6(6·0)	65·3(13·2)	0·67†
Sex ratio (M:F)	3:4	8:4	0·6‡
Liver function tests*			
Total bilirubin (mg/dl)	0·50(0·20)	0·78(0·21)	0·11†
Albumin (g/dl)	3·3(1·0)	3·7(0·2)	0·28†
Prothrombin time (s)	10·3(0·5)	10·3(0·5)	0·96†
Hepaplastin test (%)	90·0(15·8)	76·8(10·8)	0·08†
Operative parameters*			
Blood loss (g)	1144(576)	867(435)	0·72†
Operating time (min)	451(222)	320(113)	0·15†
Resected liver weight (g)	459(144)	443(186)	0·76†
Postoperative morbidity rate (%)			
All complications	57	8	0·04‡
Infective complications	43	0	0·04‡

*Values are mean(s.d.). †Student's t test; ‡Fisher's exact probability method

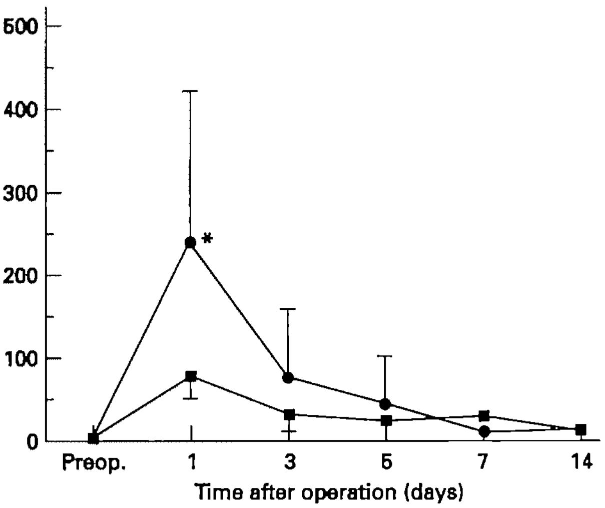

Fig. 1 Changes in mean(s.d.) serum interleukin-6 level after operation. ●, Simultaneous resection for primary cancer and liver metastases; ■, hepatectomy alone. *$P<0\cdot05$ *versus* partial hepatectomy alone (Student's unpaired t test)

($P<0\cdot05$) and rose afterwards, but failed to show any significant increase compared with preoperative values (*Fig. 2*). The postoperative concentration of serum AAT and AAG and of plasma fibrinogen was significantly lower in patients undergoing simultaneous resection than in those receiving partial hepatectomy alone ($P<0\cdot05$) (*Fig. 2*). The mean(s.d.) postoperative values for maximum level of serum AAG and haptoglobin were also significantly lower in the simultaneous resection group (81(11) *versus* 133(41) per cent and 56(19) *versus* 150(79) per cent respectively; $P<0\cdot05$, Student's unpaired t test). In all patients the maximum postoperative levels of serum AAT and plasma fibrinogen were negatively correlated with resected liver weight ($r=-0\cdot63$, $P=0\cdot03$ and $r=-0\cdot78$, $P=0\cdot003$ respectively), while those of serum AAG and haptoglobin were not affected by resected liver weight. Postoperative levels of acute-phase proteins were not affected by age, and plasma levels did not differ between patients who had infective complications and those who underwent simultaneous resection with no infection.

The postoperative ratio of acute-phase proteins : IL-6 was significantly lower in patients who had infective complications than in those who underwent partial hepatectomy alone for all measured proteins ($P<0\cdot05$, ANOVA and Fisher's PLSD) (*Fig. 3*). The ratios of AAG : IL-6, haptoglobin : IL-6 and fibrinogen : IL-6 were less than 1·0 in patients with infection.

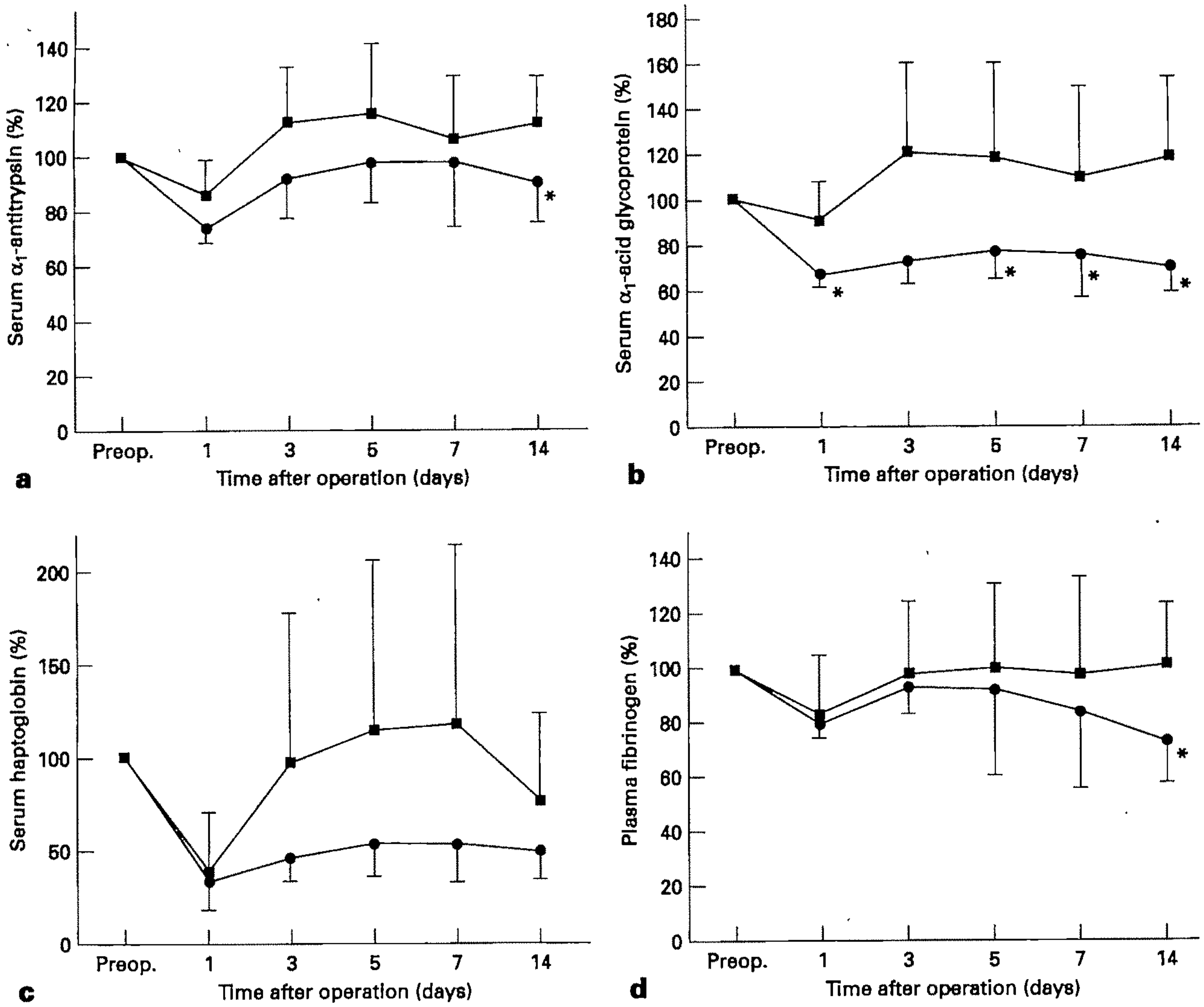

Fig. 2 Changes in the mean(s.d.) level of a serum α_1-antitrypsin, b α_1-acid glycoprotein, c haptoglobin and d plasma fibrinogen after operation, expressed as a percentage of the preoperative value. ●, Simultaneous resection for primary cancer and liver metastases; ■, hepatectomy alone. *$P<0{\cdot}05$ *versus* partial hepatectomy alone (Student's unpaired *t* test)

Discussion

The induction of acute-phase proteins is mediated by inflammatory cytokines[5]. It has been suggested that a raised serum concentration of IL-6 could reflect the severity of tissue injury caused by various diseases or surgical intervention[11–14]. It has also been reported that postoperative IL-6 levels are significantly correlated with operating time and blood loss[11,12]. In the present study, however, these two factors did not affect the IL-6 concentration. Therefore it is suggested that tissue injury resulting from bowel resection for the primary lesion might induce additional production of IL-6 and result in higher serum concentrations of this cytokine following simultaneous resection. Another possible explanation for the increased level of serum IL-6 after this procedure might be activation of macrophages and Kupffer cells by endotoxins derived from the bowel[5,15]. However, serum IL-6 levels did not differ between patients undergoing gastrectomy and those having colorectal resection. Castell *et al.*[16] reported that the liver plays a major role in the clearance of IL-6, suggesting that major hepatectomy may result in markedly increased postoperative levels of serum IL-6. However, resected liver weight was no different between the two hepatectomy groups in the present study.

Human plasma levels of acute-phase proteins have been reported to increase more than twofold during the first 5 days after elective surgical injury[5]. One reason for the reduced peak plasma concentration of these proteins after liver resection might be the decreased hepatic capacity of plasma protein synthesis as a result of reduced liver volume, because the postoperative levels of serum AAT and plasma fibrinogen correlated negatively with resected liver weight. A reduction in the hepatic capacity for plasma protein synthesis after partial hepatectomy has been also reported in rats by Milland *et al.*[7]. This reduction was suggested to be caused by increased DNA synthesis and replicative protein synthesis for liver regeneration, and so may also explain the reduced hepatic acute-phase response.

Despite the higher level of serum IL-6, hepatic acute-phase response was depressed further after simultaneous resection of bowel and liver than after liver resection alone. One possible explanation for the further depression

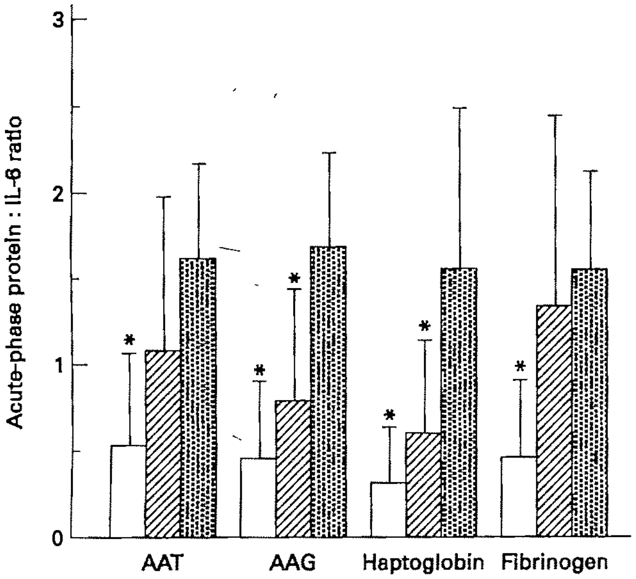

Fig. 3 Acute-phase protein : interleukin (IL) 6 ratio after operation. Values are mean(s.d.). □, Patients with infective complications; ▨, patients who underwent simultaneous resection with no infective complications; ▩, patients with metachronous metastases who underwent partial hepatectomy alone. AAT, α_1-antitrypsin; AAG, α_1-acid glycoprotein. $^{*}P<0{\cdot}05$ *versus* patients with metachronous disease (analysis of variance and Fisher's protected least significant difference)

of the hepatic acute-phase response might be endotoxaemia. Gastrointestinal resection and major hepatectomy have been suggested to bring about increased absorption and decreased elimination of endotoxins[15,17]. Because endotoxins have been reported to reduce hepatocellular protein synthesis[18,19], it is likely that simultaneous resection reduces hepatic protein synthesis. Miyazaki *et al.*[8] have also reported that simultaneous resection of the liver and bowel significantly reduces protein synthesis in the remnant liver compared with that following hepatectomy alone in rats. It has been shown that hepatic capacity for protein synthesis is reduced in the elderly[20]. However, mean age did not differ between the two hepatectomy groups in the present study. A further possibility is that the additional tissue injury caused by bowel resection for the primary lesion might result in increased consumption of acute-phase proteins.

Increase in the plasma levels of acute-phase proteins after tissue injury seems to be clearly linked to the host's ability to resist or control infection[5,6]. A number of investigators have examined the hypothesis that specific acute-phase proteins may interfere with endotoxin toxicity[21–23]. Inflammatory cytokines are associated with the pathogenesis of multiple organ failure and adult respiratory distress syndrome[9,10,24,25] and so further reduced hepatic acute-phase response and increased levels of serum IL-6 following simultaneous resection might render patients more susceptible to infection, resulting in a higher incidence of postoperative septic complications. This would explain why low acute-phase proteins : IL-6 ratios were associated with the frequent development of infectious complications.

Acknowledgements

This study was supported by grants from the Kawano Masanori Memorial Foundation for the Promotion of Paediatrics.

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British Journal of Surgery 1996, 83, 1007–1009

Emergency transhiatal oesophagectomy for instrumental perforation of an obstructed thoracic oesophagus

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Between 1986 and 1994, 14 patients underwent emergency transhiatal oesophagectomy for iatrogenic instrumental perforation of the oesophagus. Continuity of the alimentary tract was restored immediately with cervical anastomosis by oesophagogastroplasty in 13 and oesophagocoloplasty in one. Six patients had oesophageal perforation with a carcinoma, seven had corrosive strictures, and cardiac achalasia was present in one. Only five patients underwent operation within 24 h of initial trauma. There were two postoperative deaths. Resectional surgery, though aggressive, has given good results for perforations with oesophageal strictures. Transhiatal subtotal oesophagectomy has both theoretical and practical advantages over transthoracic resection in the management of instrumental perforation with a distal stricture.

Oesophageal perforation from instrumentation is a life-threatening complication. There is general agreement that its treatment demands prompt diagnosis and management. However, controversy still exists about the best method of therapy. Contained leaks that do not reach the pleura may be treated conservatively with a success rate of 100 per cent[1]. Perforation into the pleural cavity poses a real management problem. Primary repair is possible in patients who present early and have a normal oesophagus. Repair is seldom feasible when the stricture (benign or malignant) itself is lacerated. Similarly, repair of an oesophagus proximal to an undilatable stricture is likely to fail and hence is not advisable. Some authors[2–4] have advocated oesophagectomy as it extirpates the intrinsic oesophageal pathology and provides an effective control of complex fistula. In the past 8 years, 14 such patients have been treated by one-stage transhiatal oesophagectomy (THO) with cervical oesophagogastrotomy in the author's unit. These patients are reported.

Paper accepted 5 September 1995

Patients and methods

Between 1986 and 1994, 14 emergency operations for iatrogenic-free perforation of the oesophagus were performed by the author through a transhiatal approach without thoracotomy. All patients were referred from other centres and services of the hospital. There were seven men and seven women with an age range of 18–65 years (*Table 1*). The intrinsic pathology in the oesophagus was benign in eight (four men) and malignant in six (three men). Patients with benign disease were younger (18–48 years) than those with cancer (38–65 years). Perforation was caused by bougienage of a benign stricture (corrosive) in seven patients and pneumatic dilatation of cardiac achalasia in one. Five patients developed perforation during the first dilatation. Perforation of the malignant lesions followed first dilatation in four and biopsy in two. A flexible endoscope was used in all patients.

The site of the stricture and the perforation was the middle third in six patients and the lower third in eight. Two patients each had two perforations. The patient with cardiac achalasia had vertical oesophageal rupture over 12 cm. Moderate to severe pain was present in all patients, although it was ignored in some leading to a delay in diagnosis. Surgical emphysema over the chest wall was present in nine, extending up to the neck in four. The diagnosis of perforation was confirmed in all patients by water-soluble contrast oesophagogram. Mediastinal and pleural contamination was always present and peritonitis was evident in

Table 1 Clinical features and results of patients undergoing emergency transhiatal oesophagectomy

Patient no.	Age (years)	Sex	Intrinsic oesophageal disease	Interval from perforation to surgery (h)	Complications	Postoperative hospital stay (days)	Outcome
1	24	M	Corrosive stricture in middle third	< 24	RLN palsy, anastomotic leak	12	Alive and well at 7 years
2	35	M	Corrosive stricture in middle third	192 (8 days)	Respiratory failure	11	Well at 5 years
3	25	F	Corrosive stricture in lower third	48	RLN palsy; anastomotic leak	20	Well at 4 years
4	18	F	Corrosive stricture in lower third	72	Respiratory failure	8	Well at 2 years
5	28	F	Corrosive stricture in lower third	< 24	Nil	7	Well at 2 years
6	21	M	Corrosive stricture in lower third	48	—	0	Died
7	30	M	Corrosive strictive in middle third	48	Nil	10	Well at 1 year
8	48	F	Achalasia cardia	< 24	Nil	8	Well at 4 years
9	45	M	Carcinoma in middle third	< 24	Anastomotic leak	11	Survived 1 year
10	40	F	Carcinoma in middle third	72	Septicaemia	3	Died
11	38	F	Carcinoma in lower third	48	Respiratory failure	12	Survived 2 years
12	55	M	Carcinoma in lower third	48	Nil	8	Survived 1 year
13	60	M	Carcinoma in lower third	< 24	Left pyothorax	18	Survived 6 months
14	65	F	Carcinoma in middle third	48	Nil	11	Well at 9 months

RLN, recurrent laryngeal nerve

Table 2 Outcome of oesophagectomy for instrumental perforation of stenotic lesions in series published between 1986 and 1996

Reference	Year	Total no. of patients	B/M	Operation	No. of deaths
Brewer *et al.*[18]	1986	2	1/1	TT	0 (0)
Moghissi and Pender[6]	1988	11	11/0	TT	2 (18)
Yeo *et al.*[9]	1988	4	0/4	TH	0 (0)
Gouge *et al.*[23]*	1989	23	—	—	6 (26)
Flynn *et al.*[29]	1989	4	4/0	TT	0 (0)
Matthews *et al.*[2]	1989	5	0/5	TT	1 (20)
Attar *et al.*[25]	1990	9	3/6	TH ($n=3$) TT ($n=6$)	2 (22)
Orringer and Stirling[3]	1990	24	21/3	TH/TT	3 (12)
Jones *et al.*[24]*	1992	49	—	—	14 (29)
White and Morris[8]	1992	5	0/5	TT	0 (0)
Gupta (present series)	1996	14	8/6	TH	2 (14)

Values in parentheses are percentages. *Collected review. B, benign; M, malignant; TT, transthoracic; TH, transhiatal

two. The time interval between injury and surgery was less than 24 h in five, 24–48 h in six and 48–72 h in two. One patient was referred to the author's unit 1 week after the initial trauma. Intercostal drainage had been carried out in only four patients.

THO was performed by the standard technique as already described[5]. In the patient with achalasia, a left thoracotomy was performed initially with the aim of closure of the perforation and cardiomyotomy for the relief of obstruction. However, when the rupture was found to be extensive, the chest was closed and a standard THO performed. Continuity of the alimentary tract was restored by cervical oesophagogastrotomy in 13 patients. The left colon was used as oesophageal substitute in one patient (no. 6) as the stomach was scarred and contracted because of corrosive injury. The mediastinum and pleural cavities were thoroughly irrigated and bilateral chest tubes were inserted in all patients. The operation time varied from 2 h 30 min to 4 h. The amount of blood transfused ranged from 2 to 6 units.

Results

There were no complications in five patients and they were able to leave hospital within a mean 8·8 (range 7–11) days after surgery (*Table 1*). Opening of the pleural cavity, which was frequently deliberate, was not considered as a complication. None of the patients required thoracotomy as a result of excessive haemorrhage. Various complications included temporary recurrent laryngeal nerve palsy in two patients and anastomotic leak in three. One patient required ventilation after surgery for 24 h. Pyothorax had to be drained by chest tube in one. Five patients developed anastomotic stricture and underwent dilatation: one (no. 1) required multiple dilatations for 6 months. Histopathological examination of the resected specimens showed transmural infiltration with perioesophageal lymph node metastases in patients with malignant disease. Mean postoperative hospital stay was 11·4 (range 7–20) days.

There was no intraoperative death, but two patients died in the postoperative period. These two patients were referred more than 24 h after perforation (*Table 1*). A young man (no. 6) who had undergone oesophagocoloplasty for benign disease died immediately after operation. One patient with carcinoma (no. 10) died from septicaemia 3 days after surgery. All the patients with benign disease are alive and well. Of the patients with neoplasia, only one is alive at 9 months and the remaining four died within 2 years.

Discussion

Instrumental perforation of the oesophagus with distal obstruction is a complex problem. The lumen of the oesophagus is constantly in communication with the mediastinum and pleural cavity leading to their contamination with oral secretions. Thus, both chemical and bacterial invasion ensues with localized or widespread infection and, if left untreated, is usually rapidly fatal. According to the well established principle of alimentary tract surgery, a fistula is not likely to close in the presence of distal obstruction or a neoplasm. The stenotic lesion also needs to be treated together with the perforation. Resection, though aggressive, has been found to be most useful in such cases (*Table 2*). This was proven by Moghissi and Pender[6] who reported a mortality rate of 83 per cent among 12 patients with prestenotic perforations treated by various forms of conservative management (including primary closure and drainage). For the other 11, in whom the obstruction was resected, there was reduction in the mortality rate to 18 per cent. Orringer and Stirling[3] also advocated an aggressive approach of oesophagectomy by a transthoracic or transhiatal approach with primary or delayed restoration of the continuity of the alimentary tract, depending on the condition of the patient. They reported a mortality rate of 12 per cent (three of 24). Johnson *et al.*[7] successfully managed five patients with a prestenotic perforation (three malignant, two benign) by transthoracic oesophagectomy. Others have reported similar results[2,8,9].

The author concurs with Yeo *et al.*[9] and Orringer and Stirling[3] that THO is a valuable surgical alternative in the management of instrumental perforation of the oesophagus. It avoids thoracotomy in sick patients and the incidence of postoperative pulmonary complications is minimized[10,11]. There is adequate longitudinal clearance and healthy tissues are anastomosed in the neck, which is an uninfected area. A cervical anastomotic leak is more easily managed with low morbidity and mortality. Moreover, oesophagectomy also provides definitive treatment for carcinoma and most benign obstructive lesions. This view is supported by many authors[10–13]. Since 1986, one-stage THO without thoracotomy and a cervical oesophagogastric anastomosis has become the approach of choice for oesophageal resection of benign and malignant disease in the author's unit.

Bladergroen *et al.*[14] also described a favourable outcome in five patients with carcinoma and perforation treated by immediate resection. However, these authors reported a mortality rate of 66 per cent in patients who had delayed (more than 24 h) oesophagectomy. Although enhanced morbidity and mortality after delayed operation have been reported by almost all workers[15–17], this value is misleading, as nine of the 14 patients who died from resection had undergone an attempted closure of the perforation. If resection had been attempted initially, these patients might have survived. In the present series, both patients who died were referred for surgical consultation after more than 24 h. Brewer *et al.*[18] and Orringer and Sterling[3] emphasized the need for a two-stage operation (delayed reconstruction of the alimentary tract) in two sick patients undergoing delayed surgery. Such an approach may have been appropriate in patient no. 6. Management must be tailored to an individual patient's need[19].

Reluctance to perform major surgery in the management of instrumental perforation of an obstructed thoracic oesophagus has resulted in some conservative procedures. The relief of distal obstruction by the placement of prosthetic tubes has led to high mortality rates (32–78 per cent)[20–22]. The method of exclusion diversion, which entails a cervical oesophagostomy, exclusion of the thoracic oesophagus at the cardia, gastrostomy and feeding jejunostomy, has also been found to be unsatisfactory[21,23–27].

Perforations following pneumatic dilatation of achalasia are more common (2–5 per cent)[22] and are usually treated by closure and myotomy to relieve obstruction[4,22,28,29]. The solitary case in the present series was treated by oesophagectomy as initial thoracotomy revealed an extensive longitudinal tear.

To summarize, obstruction was a key factor in the cases of oesophageal perforation discussed. Another striking factor was the delay in the referral of patients. It is suggested that THO is a reasonable surgical option in the management of instrumental perforation of the oesophagus.

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British Journal of Surgery 1996, 83, 1010–1019

Correspondence

Clinical biology of nitric oxide

Sir

In the review by Mr Davies and colleagues[1] (*Br J Surg* 1995; 82: 1598–610) it was concluded that 'nitric oxide (NO) appears to play a significant role in the physiology and homoeostasis of many of the body's systems. Its role in pathophysiology of disease remains to be fully elucidated. It is unclear whether alterations in NO production or release and degradation are primary events in a pathological process or sequel of an as yet undefined primary insult'.

The multiple properties of nitric oxide are a major challenge when an attempt is made to integrate its diverse functions into the mechanisms that produce the greater part of the physiological and pathological conditions in the human organism.

Regarding the acute inflammatory response to injury by mechanical energy, we have recently proposed that, whether local or systemic, this is based on the successive functional predominance of the nervous, immune and endocrine systems. This hypothesis implies that the final and prevalent functions of these systems may represent the consecutive phases of the response to stress developed by a single system: the psycho-neuro-immune-endocrine system[2,3].

If we consider that these functions are expressed by the endothelium and, by extension, the vascular wall, the post-traumatic local inflammatory response would include a nervous or immediate phase, with vasoconstriction and vasodilatation with ischaemia–reperfusion injury. There would then be an immune or intermediate phase, with exudation secondary to an increase in endothelial permeability, which is the cause of swelling and diapedesis or cell migration, especially of neutrophils, which is associated with phagocytosis and necrosis. This would be followed by an endocrine or late phase, characterized by proliferation with endothelial and vascular wall modelling in which, if the evolution has been favourable, anabolism and tissue regeneration or wound repair[2]. In addition, in the systemic response to injury by mechanical energy, as in the polytraumatized patient, the nervous or immediate phase would be represented by shock and ischaemia–reperfusion; the immune or intermediate phase would be characterized by the systemic inflammatory response syndrome; and the endocrine or late phase would be represented by anabolism in the convalescence period[2].

The hypothetical similarity of the local and systemic responses could be attributed to the existence in the organism of a general response mechanism to injury, which is based on the successive and predominant expression of the nervous, immune and endocrine functions. In this scheme, the functions that characterize each phase of response make it possible to integrate current biochemical knowledge about conditions considered as diverse, such as traumatic injury[2], heart failure[4], pulmonary and arterial hypertension[5], and rejection in organ transplantation[6].

In this proposal, nitric oxide would be closely regulated at every step of the acute inflammatory response according to the predominant function in the different phases which make up this response. So, in a first immediate or nervous phase, nitric oxide is a mediator of analgesia[7], contraction or relaxation of the vascular smooth muscle, myocardial contractility, bronchodilatation, relaxation of gastrointestinal smooth muscle and neurotransmission[1]. In the intermediate or immune response to injury, this molecule would be involved in capillary permeability, platelet adhesion and aggregation, leucocyte adhesion and cytotoxicity of macrophages[1]. And finally, in the late or endocrine phase, nitric oxide would be involved in endothelial regeneration and smooth muscle cell proliferation[1,8].

If nitric oxide successively expresses functions considered as nervous, immune and endocrine, in a similar way to the endothelium and, by extension, the vascular wall during the inflammatory response, it may be necessary to enlarge our current concept of the nervous, immune and endocrine systems. This notion is not limited to these systems; the whole organism is involved. These systems, however, make up a systemic response integrated by the characteristics of the nervous, immune and endocrine systems[2,3,6]. This functional concept implies that the cells and biochemical components of the organism, for example nitric oxide, have the property of modifying functional expression in the successive phases of response to injury. For this reason the characteristics of each phase of this response might make it possible to integrate current biochemical knowledge into the evolution of many diseases and thereby into the clinical evolution of a patient[5,6].

Finally, it is tempting to suggest that the succession in expression of the nervous, immune and endocrine systems might represent an ancestral response. The efficiency of this response may have made it possible for the organism to exist on the level of cells, tissues, organs and individuals, in both normal physiological situations and pathological ones[2,3,5].

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Authors' reply

Sir

The letter by Dr Arias and colleagues raises an interesting hypothesis that a psycho-neuro-immune-endocrine system is involved in the local and systemic manifestations of the inflammatory response to mechanical injury and that this system is unified through the nitric oxide pathway that can modify the successive phases of the response. The literature referenced is neither substantial nor diverse. Further experimental work will be required to support this hypothesis. There is no contention that neurohumoral, immunological and endothelial components are involved in the systemic inflammatory response syndrome (SIRS) and that each of these systems is interlinked directly or indirectly. Currently, however, there is no literature to support a hypothesis that nitric oxide is a prime mover in SIRS; rather, the literature would suggest that nitric oxide is one of several mediators involved in a series of interlinked cascades which lead to the manifestations of SIRS. Therefore, we continue to contend that it remains unclear whether alterations in nitric oxide production or release and degradation are primary events in a pathological process or sequel of an, as yet undefined, primary insult.

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A better bridge for loop stomas

Letter 1

Sir
We read with interest the article by Mr Cochrane and colleagues (*Br J Surg* 1996; 83: 365) describing the use of a deep-tension suture as a bridge for loop stomas. Their diagram shows the device in use with a loop ileostomy. It is our experience that it is unnecessary to use a bridge for loop ileostomies. If fashioned without tension they heal without significant retraction. We do, however, employ a bridge for loop colostomies and use a different, equally simple, technique. A standard 16-Ch nasogastric tube (or similar piece of available tubing) is passed under the loop of colon, and the shortened ends are joined together above the bowel with a single nylon suture. This arrangement is cheap, acts as an effective bridge and, like the device described by Cochrane *et al.*, does not add bulk to the stoma, thus allowing standard bags to be applied immediately.

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Letter 2

Sir
Mr Cochrane *et al.* described an elegant bridge for a loop stoma (*Br J Surg* 1996; 83: 365). A tight seal between bag flange and stoma is particularly important when an ileostomy is formed. We would like to draw attention to a method which has proved particularly useful for construction of a loop ileostomy. A trephine is fashioned at a previously marked site, and an appropriate loop of ileum selected. A small hole is made at the border of the mesentery, at the apex of the loop, and a fine (12-Ch) nasogastric tube is threaded through it. The tube is then passed through the trephine, and gentle traction allows the ileal loop to follow. Any abdominal procedure is completed and the laparotomy wound closed. The ileal loop can then be opened and a spout on the afferent limb formed[1]. After the mucocutaneous junction has been sutured, the nasogastric tube is cut with scissors just to either side of the loop. A non-resorbable suture secures each end of the tube bridge to the skin. The nasogastric tube thus serves not only to support the stoma, but also provides an atraumatic means by which the bowel can be delivered through the trephine.

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Endoscopic drainage aborts endotoxaemia in acute cholangitis

Letter 1

Sir
We read with interest the article by Dr Lau and colleagues (*Br J Surg* 1996; 83: 181–4). The authors report a clinical trial in patients with acute calculous cholangitis, looking at the effect of endoscopic drainage on endotoxin levels and the relationship with clinical parameters. The results showed a significant reduction in endotoxin levels after drainage, and a significant association between both bile and serum endotoxin concentration and clinical features of severe cholangitis. No correlation was found between endotoxin and biochemical parameters, such as bilirubin or alkaline phosphatase.

The results of this study are interesting, and there is no doubt that cholangitis may be complicated by endotoxaemia. It is less certain that the circulating endotoxin concentration is quantitatively correlated to disease severity, as described in some studies[1,2]. Although previous studies have indeed found that the presence of endotoxin did correlate with disease outcome, no clear dose–response relationship between levels of endotoxin and disease severity were detected[3,4]. In fact, some studies have failed to show that circulating endotoxin levels predict clinical outcome[5]. Additionally the presence of endotoxin in the limulus amoebocyte lysate (LAL) assay would probably not have changed the management of the patient.

The study by Lau *et al.* suggests that the initial endotoxin level has predictive value in the severity of cholangitis. However, *Fig. 1a* giving serum endotoxin levels appears to show data obtained in a subgroup, probably the 19 patients with detectable (very high) serum endotoxin levels, and it is only in these critically ill patients that clinical symptoms (Charcot's triad) appeared to correlate with endotoxaemia. These conclusions do not necessarily apply to the entire group. Nonetheless, we do agree that bile duct infection and an inflammatory response are related. We recently performed a study looking at the inflammatory response during an acute attack of cholangitis, and again after subsequent treatment. We did not find a uniform significant reduction of the plasma endotoxin concentration measured by the LAL assay after endoscopic and antibiotic treatment, and the levels in our patients were much lower (approximately by 10 to 100 times) than those reported by Lau *et al.*, in which the mean serum levels were approximately 400 pg/ml. Endotoxaemia is a transient state as endotoxin in blood is neutralized very quickly by endotoxin binding proteins and lipoproteins, which may not all be removed by heating, and it is rapidly cleared from the circulation. We have found previously that the presence of bilirubin in plasma may cause false-positive limulus assays. This can be avoided by using plasma controls in the LAL assay to ensure that the intrinsic colour of jaundiced plasma does not interfere with this chromogenic assay, leading to an overestimation of the endotoxin levels; it is therefore important to know whether these controls were used in the present study.

On the other hand, in our patients with cholangitis, we did find a significant reduction of the cytokines tumour necrosis factor (TNF), soluble TNF receptors and interleukins in all patients. Hence this finding supports the conclusions of Lau *et al.* that cholangitis is clearly associated with an inflammatory reaction which favourably responds to endoscopic treatment. We do doubt, however, whether measurement of plasma endotoxin levels is the most sensitive assay to monitor this inflammatory response, and it remains to be demonstrated that detection of endotoxaemia would alter clinical management.

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Authors' reply

Sir

We thank Dr Kimmings and colleagues for their comments. In our article, an association was found between serum endotoxin level and disease severity but no clear dose–response relationship was demonstrated. There is disparity in the literature on the correlation between serum endotoxin level and clinical course.

A spectrum of disease severity was found in the patients. Patients with 'floating' stones did not show a significant serum endotoxin level, while endotoxaemia in those with impacted stones was severe. Comparison between groups of patients is difficult without background information. Variations among batches of limulus amoebocyte lysate assays are known to occur. The trends in endotoxin level were more important than the absolute values. The falls in both serum and bile endotoxin levels after endoscopic drainage were overwhelming in these patients. We agree that jaundiced serum can lead to high spectrophotometric readings. Two control plasma samples were run in parallel for each endotoxin determination.

Dr Kimmings and colleagues are putting the cart before the horse. We are not advocating the use of serum endotoxin for disease monitoring. Clinical signs in association with endotoxaemia should dictate the need for urgent endoscopic drainage.

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Letter 2

Sir

We read with interest the paper by Dr Lau and colleagues (*Br J Surg* 1996; 83: 181–4) describing endotoxaemia in 40 patients with acute cholangitis, and its reversal following endoscopic biliary drainage. In addition, they reported an association between the initial bile and serum endotoxin concentrations and the severity of cholangitis.

Both biliary obstruction and the presence of infected bile are necessary elements of acute colangitis[1]. Portal and systemic endotoxaemia is well documented in patients with biliary obstruction[2]. Since Wardle and Wright[3] first reported an association between endotoxaemia and renal dysfunction in jaundiced patients in 1970, endotoxin has been increasingly implicated in the pathophysiology of the complications of obstructive jaundice.

We have previously demonstrated reversal of portal and systemic endotoxaemia following both internal and sterile external biliary drainage of jaundiced rats[4]. Gouma *et al.*[5] have also shown reduced endotoxin concentrations following experimental internal biliary drainage. It is postulated that returning bile salts to the gastrointestinal tract reduces the endotoxin pool available for absorption into the portal circulation due to their antiendotoxic properties[6]. Decompression of the obstructed biliary tract improves Kupffer cell phagocytic function and promotes clearance of endotoxins from the circulation[7]. These mechanisms may be synergistic in reversing endotoxaemia and its clinical effects. In the present study, endoscopic biliary decompression dramatically reduced bile and serum endotoxin levels, thus supporting the concept that internal biliary drainage reverses endotoxaemia.

Endoscopic biliary drainage is advocated by many authors as the treatment of choice for patients with severe acute cholangitis secondary to choledocholithiasis[8–11]. Boender *et al.*[12] recently reported that the risk of complications from cholangitis rose with increasing delay between the onset of cholangitis and biliary drainage[12]. Therefore we would agree with the authors that patients with severe acute cholangitis, or those whose clinical condition deteriorates despite adequate conservative treatment, warrant urgent endoscopic biliary decompression.

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Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation

Sir

We read with interest the results of the SCOTIA study group (*Br J Surg* 1995; 82: 1622–7). Because of its occasional need for a permanent stoma the first method was not as successful as the second. The authors note that the technical challenge associated with new methods is often avoided, and that the two-stage Hartmann's procedure therefore remains a popular procedure. Hartmann's method, however, is still unsatisfactory as in 32–60 per cent of cases the stoma is never reanastomosed.

The paper did not mention a suitable alternative to the two-stage operation: a transverse colostomy for treating obstruction, colonoscopic exploration and then a second operation with radical segmental resection and anastomosis and simultaneous closure of the stoma. The early closure of the stoma, possibly by segmental resection, is made easier through the combined internal and external access and, according to our experience, does not result in the known, high morbidity rates of early stoma closure. This operative tactic is based on technical progress in the construction of an anastomosis and the safety of simultaneous double resections. Permanent colostomy or a three-stage procedure are needed only in exceptional cases when a protective stoma is necessary anyway (i.e. with a very low anastomosis).

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Conservative treatment *versus* antireflux surgery in Barrett's oesophagus: long-term results of a prospective study

Sir

The article from Professor Parrilla's group (*Br J Surg* 1996; 83: 274–8) is important, but its conclusion needs clarifying.

It demonstrates that successful antireflux surgery may reduce the risk of neoplasia in Barrett's oesophagus compared with traditional conservative therapy, namely lifestyle changes, diet, postural measures and H_2 antagonists. It does not, however, demonstrate what effect successful acid suppression has on the neoplastic potential of Barrett's mucosa. Omeprazole was not taken by the 'conservative group' until 1992, 10 years after this study began. In addition, only a symptom score was performed to assess the efficacy of the medical treatment. These patients should have had pH monitoring repeated while on medication. Correlation between symptoms and acid suppression is notoriously unreliable and even omeprazole does not always abolish acid reflux[1].

If pH monitoring had confirmed adequate acid suppression in the medically treated group (which I doubt) one might conclude that the higher incidence of neoplasia was due to duodenogastric reflux. As it stands, we do not know which components of the refluxate are likely to be responsible for the observed differences.

Antireflux surgery seems a good option for patients with Barrett's oesophagus but proton pump inhibitors may be just as good. Only further prospective studies will tell us the answer.

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1 Katzka DA, Castell DO. Successful elimination of reflux symptoms does not insure adequate control of acid reflux in patients with Barrett's esophagus. *Am J Gastroenterol* 1994; 89: 989.

Authors' reply

Sir

Many thanks to Mr Hardwick for his interesting comments on our paper. We agree with him in that our paper does not show conservative treatment to achieve successful acid suppression, as we did not perform pH-metric studies in these patients. However, as he himself states, even omeprazole does not always prevent reflux. Moreover, in usual clinical practice it is not common to perform pH-metric controls in these patients to ensure that acid suppression is efficient. Furthermore, potential neoplasia could be related to duodenogastro-oesophageal reflux which, although lessened with omeprazole in that it reduces the volume of gastric contents, does not disappear completely[1]. In any case the aim of this paper, as mentioned in the final conclusion, is simply to question the advantages of the systematic conservative approach in the initial management of patients with Barrett's oesophagus, especially in young patients, because lifetime medication will be necessary.

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Value of routine intraoperative cholangiography in detecting aberrant bile ducts and bile duct injury during laparoscopic cholecystectomy

Sir

We read with interest the article by Dr Kullman and colleagues (*Br J Surg* 1996; 83: 171–5). This article inflames the continuing debate on selective *versus* routine cholangiography, initiated by Mirizzi[1] in 1937. It is now clear that the initially high incidence of bile duct trauma on the introduction of laparoscopic cholecystectomy was due to the steep learning curve associated with the new skills required for this technique.

The argument in favour of routine cholangiography proposed by the authors was clarification of biliary anatomy, and they wished to assess operative cholangiography as an adjunct in the prevention of biliary tract injury. In the patients presented, a selective policy would have dictated the use of operative cholangiography in patients 2 and 3 because of obscured anatomy. Laparoscopic cholecystectomy for acute cholecystitis is controversial and many surgeons would not advocate it in this situation; however, if performed in the presence of acute inflammation this would be a relative indication for cholangiography. Cholangiography led to bile duct injury in patient 1 and possibly in patient 2, both necessitating T tube drainage. The operative cholangiogram in patient 2 was performed during the open operation, not during the laparoscopic procedure and therefore cannot lend weight to the argument for routine intraoperative laparoscopic cholangiography. The cholangiogram in patient 2 was performed to confirm the anatomy obscured by severe inflammation. The normal anatomical arrangement had been demonstrated at preoperative endoscopic retrograde cholangiopancreatography (ERCP), but this knowledge did not prevent injury in this case.

We believe, with the advances in non-invasive imaging and minimally invasive techniques (ERCP) combined with preoperative biochemical evaluation by liver function testing, that a selective policy is favourable. We concede that the debate is ongoing.

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Author's reply

Sir

We thank Dr Fligelstone and colleagues for their interest in our study. As pointed out in the article, apart from the aid of identifying unsuspected common bile duct stones, the main purpose with routine intraoperative cholangiography, be it during open or laparoscopic cholecystectomy, is to delineate the biliary anatomy.

According to the literature, the pattern of bile duct injury associated with laparoscopic cholecystectomy is almost identical to that in open cholecystectomy, i.e. the duct is damaged at the level of or above the entrance of the cystic duct. The most common type of injury occurs when the surgeon mistakes the common duct for the cystic duct, transects or ligates it, and excises the extrahepatic biliary tree along with the gallbladder. As shown by patients 1 and 2 in our series, this injury may be avoided if the principle of never transecting a duct until it has been identified is followed.

It seems that Dr Fligelstone and colleagues have misunderstood some of the results in our study. Intraoperative cholangiography did not lead to any bile duct injury or other complication. On the contrary, thanks to the routine use of cholangiography, at least two severe bile duct injuries were avoided. In patients 1 and 2 the surgeons mistook a slender common duct for the cystic duct. The ducts were partially opened but the mistakes were recognized at cholangiography, i.e. the cholangiogram served as a 'road map' and prevented transection of the common duct in both cases. Repair of the small ductotomies was undertaken by closing the defect and inserting a T tube. No late sequelae occurred.

Based on the results from this and other studies, we think there is convincing documentation that routine use of intraoperative cholangiography decreases the incidence and severity of bile duct injuries in both open and laparoscopic procedures. We also believe that there is no value in performing preoperative endoscopic retrograde cholangiopancreatography (ERCP) to delineate the biliary anatomy. Acute or chronic inflammatory changes often distort the biliary anatomy, but this is not revealed at preoperative ERCP, i.e. a normal retrograde cholangiogram probably tells nothing about what operation might reveal. The advantage of preoperative ERCP is to be able to diagnose and treat common bile duct stones, but its preventive value is limited. How preoperative evaluation of liver function test results would prevent bile duct injuries is a mystery to us.

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The future of surgical journals in the electronic publishing era

Sir

The leading article by Mr Young (*Br J Surg* 1996; 83: 289–90) raises two important issues needing wider discussion within the medical profession.

Attention is drawn to the volume of information which can become available on the Internet and it is rightly pointed out that if editors do not publish material it may reach the Internet via alternative 'publishers'. The National Health Service (NHS)-wide net, in theory for the use of the NHS only, will face a similar problem unless some form of editorial control is placed on material to appear before a wide audience. While medical sceptics may learn to ignore the inaccurate, the fear must be access by the public to non-reviewed and inconsequential material. One can just keep pace with *The Times* newspaper, but it will be impossible to face patients who have gained access to published misinformation on the Internet. Some form of accreditation of work to be placed in the public domain will be essential.

The second and much more complex issue is the provision of a bedside terminal connected to this information highway. In the present state of medical computing it would be most unwise for any connection to be made to an outside network such as the Internet or, for that matter, JANET from clinical systems.

It is, perhaps, merciful that such is the state of hospital computing and information that accredited users have extreme difficulty extracting worthwhile information. When we do and when the links are made, the security of that information is going to be of prime importance.

At present it is hoped that simple departmental systems will let us get CD-ROM (compact disk–read-only memory) information from the *British National Formulary*, Medline and your journal with no wider connection necessary.

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Bilateral gracilis neosphincter construction for treatment of faecal incontinence

Letter 1

Sir

We were interested to read the recent paper by Mr Kumar *et al.* (*Br J Surg* 1995; 82: 1645–7). We are impressed with the results reported, particularly bearing in mind the heterogeneity of the patients with regard to their underlying aetiology. Both we at the Royal London Hospital and Baeten and colleagues in Maastricht have found the efficacy of the electrically stimulated gracilis neosphincter (ESGN) procedure very variable between different patient groups. The results are significantly poorer in patients with a congenital aetiology and in those who have undergone abdominoperineal excision of the rectum[1,2]. This fact is not surprising as the procedure only attempts to correct a sphincteric defect. These patients also lack the normal sensory apparatus, rectal reservoir and evacuatory mechanisms essential for normal continence. In contrast to patients with an ESGN, where the muscle is continuously stimulated except during defaecation, the unstimulated graciloplasty requires volition to evoke contraction. If continence is to be preserved a sense of imminent evacuation is essential. Did the authors conduct any objective physiological tests or subjective evaluation of patients' anorectal sensory function?

We acknowledge the importance of encircling the entire anal canal with healthy muscle rather than tendon. In contrast to the authors we do not find this a problem using a single gracilis muscle. The transposed gracilis is tethered by its proximally based vascular pedicle. By mobilizing these vessels maximally, it is possible to gain sufficient muscle length to encircle the anal canal entirely without undue tension on the pedicle.

The postoperative resting pressures in the patients are high, and it may be that the muscle is acting like a biological Thiersch wire. This situation is in contrast to the ESGN, where basal pressures (when the muscle is not stimulated) are not significantly altered by the procedure and where the muscle acts as a truly dynamic sphincter[3]. It would be interesting to know at what time after the procedure the measures were made and whether there was any alteration in the resting and squeeze pressures over time. This would provide conclusive evidence regarding the question of muscle atrophy following transposition.

We acknowledge that this technique obviates the need for expensive electrical hardware but would contest that it enables construction of a neosphincter in a more physiological manner. Despite initial enthusiasm for the technique from Pickrell *et al.*[4], the unstimulated graciloplasty procedure has not stood the test of time. Similarly the two glutei muscles have been used in a similar construction to that described in Kumar *et al.*'s paper. This technique has also not proved any more successful than the unstimulated graciloplasty[5]. The problems of muscle fatigue and difficulty in producing voluntary contraction are likely to remain with the new technique. The introduction of chronic long-term electrical stimulation has overcome these limitations.

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Letter 2

Sir

We read with interest the paper by Mr Kumar and colleagues (*Br J Surg* 1995; 82: 1645–7). Bilateral graciloplasty was used to treat patients with severe faecal incontinence. Excellent results were reported: in nine of ten patients continence was achieved.

However, we wonder how faecal continence was achieved because a sustained voluntary contraction of the double graciloplasty seems mandatory to postpone defaecation. In addition, the gracilis muscles are prone to fatigue and incapable of maintaining prolonged (sphincteric) contractions[1].

In a study of 52 patients with intractable faecal incontinence treated with a single electrically stimulated (dynamic) graciloplasty, 38 (73 per cent) were continent after a median follow-up of 2·1 years. The ability to postpone defaecation increased from 9 s to 19 min, and the enema retention time increased from 0 to 3 min after 1 year of follow-up[2]. Defaecography was used to quantify anal canal closure and demonstrate sphincteric action[3]. Magnetic resonance imaging (MRI) after gracilis transposition demonstrated a 33 per cent reduction in muscle diameter, which did not correlate with continence. The value of MRI in five of ten patients in Mr Kumar's series remains questionable, therefore[4]. It is unclear why joining the two muscles in the midline would prevent atrophy. In our opinion, continence after dynamic graciloplasty is due to an electrically induced conversion from type II (fatigue-prone) into type I (fatigue-resistant) muscle fibres, which allows sphincteric action independent of a voluntary contraction[1,2].

The reconstruction of the anal sphincters by using a double graciloplasty has been, in our experience, a promising technique for the creation of a neosphincter after abdominal resection for rectal cancer. However, continuous electrical stimulation by using implanted electrodes and a pulse generator was mandatory to achieve a life without stoma[5]. Nevertheless, surgical techniques that avoid the implantation of foreign material deserve to be studied.

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Authors' reply

Sir

Thank you for giving us the opportunity to reply to the points raised by Messrs Mander and Williams. We did not perform any objective physiological tests, but asked all our patients about the sensation to defaecate. They were all able to perceive the sensations of rectal fullness and the desire to evacuate, but we take the point that objective sensory function evaluation needs to be performed.

Mander and Williams are quite right to question the viability of the muscle, particularly in the long term, and we were aware of this problem. To address this question, we performed magnetic resonance imaging (MRI) in five of our patients and, in fact, have gone on to perform MRI in the remainder as well. We are happy to report that signal strength from the neosphincter does not appear to change even 3 years after operation. We believe that this fact provides better objective evidence of muscle viability than longitudinal pressure measurements.

It is true to say that the single muscle unstimulated graciloplasty has not fulfilled all expectations, but many of the failures can be attributed to technique. As regards the long-term results, even the stimulated graciloplasty has to prove its worth.

Regarding the comments kindly provided by Dr Baeten and his colleagues, it is true that the gracilis muscle is prone to fatigue and incapable of maintaining prolonged contractions, but it is also true that the muscle is not called on continuously to maintain a chronic state of contraction. Continence is achieved by several factors that include rectal function, colonic transit and sphincteric function. Therefore in patients with normal rectal and colonic function, the contribution of the external sphincter or neosphincter in the maintenance of continence is only required for deferment of defaecation when circumstances are not suitable. We used MRI to assess the viability of the muscle rather than correlate muscle diameter with function because we believe that this is a relatively non-invasive way of looking at muscle viability.

We joined the two muscles in the midline for two reasons: first, to gain mechanical advantage in the same way as other pelvic floor muscles are inserted into each other, and second, with the insertion of the two muscles into one another there will be minimal risk of muscle atrophy following disconnection of the tendon from its insertion.

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Incidence of third-degree perineal tears in labour and outcome after primary repair

Sir

We wish to congratulate Mr Walsh and his colleagues (*Br J Surg* 1996; 83: 218–21) on highlighting the issue of third-degree tears in what is one of the few prospective reports of such a problem. They report on the incidence and outcome of third-degree tears after 16 583 vaginal deliveries, which were prospectively assessed over a 5·5-year period.

They comment that 93 women sustained a third-degree tear (0·56 per cent). In terms of outcome, 20 per cent ($n = 81$) of those reviewed at 3 months postpartum reported anal incontinence. They go on to project that the overall incidence of faecal incontinence in the 16 583 deliveries was 0·04 per cent. This figure is almost certainly not representative of the incidence in the overall population, simply because they have not assessed all of the women who did not have a third-degree tear. Indeed, the incidence may be much higher. Incontinence of faeces or flatus is a debilitating and embarrassing condition, and many women who suffer from it will not readily offer this information at postnatal or later consultation. They need therefore to be questioned directly at postpartum follow-up. This is all the more important, if we are to accept the recent data showing anal sphincter disruption after vaginal delivery in approximately one-third of primiparous women[1].

Walsh *et al.* go on to report that third-degree tears were significantly associated with the use of forceps. They do not mention use of the ventouse, which has minimal associated risk of third-degree tear compared with forceps[2,3]. It has been suggested that the ventouse should be the instrument of choice for operative vaginal delivery[4], and this applies particularly to low and outlet instrumental deliveries. Was the ventouse used for any of the instrumental deliveries during the study period?

The authors comment that the repairs were performed by obstetric senior house officers and registrars. Although the information is not available, we believe that the majority of obstetric units in the UK would recommend that third-degree tears should be repaired by someone of registrar status, at least. It raises the question, however, as to who exactly should perform these repairs, and indeed whether colorectal surgeons should have a greater involvement, particularly for complicated third-degree tears.

Despite these comments, we believe Walsh and colleagues should be commended for focusing attention on an obstetric problem that is an uncommon but very serious complication of vaginal delivery. The paucity of prospective randomized trials on various aspects of management of third-degree tears needs to be highlighted. It remains unclear, for example, what suture material should be used at initial repair; whether or not prophylactic antibiotics should be used; whether stool softeners or high-residue diet should be implemented in the first week or so after childbirth; and finally, whether or not elective episiotomy should be performed at future deliveries in an effort to prevent a further third-degree tear. We await the results of such findings with interest.

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Authors' reply

Sir

We thank Mr Geary and Miss Mellon for their interest in our work. We entirely agree that the incidence of incontinence, particularly for flatus, is likely to be underestimated in our study as we only examined the patients most likely to be injured, i.e. those sustaining a third-degree tear. It is likely that some of the women sustaining lesser injuries whom we did not examine will also be symptomatic. We focused our efforts on those most likely to be injured. One of the benefits of the routine visit to our colorectal clinic has been to detect all those women who are incontinent without embarrassment for them. We have also found that a number of women who have been asymptomatic (but with abnormalities on examination) when first seen in the clinic have come back of their own accord when they started to develop symptoms.

The ventouse extractor has been used increasingly in the latter part of the study period and subsequently. We are now seeing a number of patients who have sustained a third-degree tear when forceps have been used after a failed ventouse extraction, and a small number after ventouse extraction alone.

The initial repair of third-degree tears is frequently carried by obstetricians in training. During this study one of us visited the labour ward to witness a primary repair of a third-degree tear. The disruptive nature of the injury made precise reconstruction of the individual components of the sphincter impossible, and simple reapproximation of the visible muscle was performed. It would have been impossible to perform the overlapping technique used by coloproctologists in delayed repair. One could speculate that a patient presenting with a similar injury as a result of a road traffic accident would most likely be treated by defunctioning colostomy.

During the study period we recommended that obstetricians change from chromic catgut to longer-lasting absorbable sutures and they now use Maxon (Davis and Geck, Gosport, UK). It is our impression that the incidence of poor outcome has diminished since this change in practice, and this matter will be the subject of a further study. We routinely use antibiotics (a single intravenous dose of cefuroxime and metronidazole) at the time of delayed repair, and it would seem reasonable to use similar prophylaxis at the time of primary repair. Stool softeners are also appropriate. In our assessment clinic we do consider the subject of further deliveries. Patients having a delayed repair for frank incontinence are advised to have a caesarian section to avoid damage to the repair. Those with physical signs and low anal canal pressures are advised to consider seriously caesarian section, and those who have a normal examination are advised to have a further vaginal delivery but to remind all taking part in their obstetric care that they have previously sustained a third-degree tear.

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Mammary duct ectasia–periductal mastitis complex

Sir

I was surprised by a number of statements in the recent review by Mr Webb (*Br J Surg* 1995; 82: 1300–2).

If periductal mastitis and duct ectasia are connected, and present evidence indicates they might not be[1], then periductal mastitis precedes mammary duct ectasia[2], and it would have been more appropriate for the title of the article to be periductal mastitis–duct ectasia.

The first sentence states that it is the second commonest benign disease; as far as symptoms are concerned, it certainly is not[2].

There is now general agreement that periductal mastitis affects mainly young women and is associated with the development of non-lactating abscesses and mammary duct fistulas[3–6], whereas mammary duct ectasia affects an older age group, is present in over 50 per cent of women after the age of 60 years and is likely merely to represent a feature of breast involution[3,7].

Both aerobic and anaerobic bacteria have been isolated from periareolar abscesses[8,9] and mammary duct fistulas[4,10] associated with periductal mastitis. The current antibiotic of choice is co-amoxyclav[11,12] and not, as stated, flucloxacillin and metronidazole combined.

Mr Webb listed a few simple practical points, most of which I would take issue with. I would support all the points raised by Mr Bundred in his recent correspondence[13]. I would also like to raise further concerns specifically.

(1) In relation to his third practical point, non-lactating breast abscesses can be divided into those that occur in the central periareolar region and those in the periphery of the breast[11]. If pus is obtained on aspiration the correct treatment is aspiration of all the pus combined with appropriate antibiotic therapy, or mini-incision and drainage following application of local anaesthetic cream[11]. Only in recurrent periareolar abscesses is more extensive surgery likely to be necessary. It has not been my experience that peripheral abscesses recur unless associated with granulomatous lobular mastitis, and few of these peripheral abscesses need any surgical intervention following aspiration or mini-incision and drainage.

(2) It is no longer appropriate to suggest that abscesses should be treated with drainage and packing. Both lactating and non-lactating abscesses can be treated either by aspiration, combined with oral antibiotics, or limited incision and drainage without packing[11,14,15].

(3) Mr Webb suggests that it is more appropriate in menopausal and postmenopausal women than in younger women to perform total duct excision. Experience demonstrates that most patients with recurrent sepsis are young premenopausal women and that abscess formation decreases with age. Young patients with recurrent infection often have nipple inversion, so breast-feeding from the affected breast is not possible. It is illogical, therefore, to treat older patients in a different way to younger patients. Our own and other published data do not support his view that, after major duct excision, the success rate of this procedure is modest[16]. We have recently sent a questionnaire to 88 patients who underwent total duct excision. Some 94 per cent were satisfied with the outcome of the operation and only six patients required any further surgery: four for cosmetic reasons and two because of further infections. Repeat operation is, therefore, rarely necessary if the procedure is carried out correctly under appropriate antibiotic cover[11,17]. From the last 30 000 patients who were seen in the Edinburgh Breast Unit, there has been no patient who has required mastectomy for recurrent sepsis. In three patients we removed the nipple and areola complex, and I am surprised that mastectomy is ever necessary.

(4) I am not clear what Mr Webb means by 'underpinning the residual ectatic ducts following total duct excision'. It is not something I ever do after total duct excision and, as stated above, a recent audit demonstrates that our results for this procedure are satisfactory. It is disappointing that Mr Webb does not outline the current optimal method of surgical treatment of mammary duct fistulas and/or recurrent periareolar sepsis. Fistulas and recurrent periareolar sepsis are best treated by total duct excision or occasionally by excision of the diseased duct alone, combined with excision of any fistula tract if present, with primary closure of the wound under appropriate antibiotic cover[4,5,11,18].

(5) I am not clear what the author means by a 'tender para-areolar breast cyst'.

There is now clear evidence that smoking has a major role in the aetiology of periductal mastitis, but recent evidence indicates that patients with duct ectasia are not more likely to smoke than the general population[1].

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aetiologies. *Br J Surg* 1996; 83: 820–2.

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Author's reply

Sir

I am grateful for the opportunity to reply to Mr Dixon's criticisms. Some of his comments will have been addressed coincidentally in my reply to Mr Bundred.

Regarding the title, I have no strong feelings; periductal mastitis–duct ectasia complex is quite acceptable. However, the possible distinction between these components is not yet established, and it is common knowledge from published illustrations[1] and countless histopathological specimens that they are associated. Clinically, uncomplicated palpable duct thickening is equally evident in women under 40 years of age as in those above. In his paper with others[2], Mr Dixon comments on a possible sequence of events: 'Periductal inflammation, which then resolves, leads on to secondary duct fibrosis and dilatation'. Yet so often gross duct dilatation and periductal inflammation in all stages of activity are seen to coexist. The other theory of causation[3] is equally tenable.

My editorial in no way contradicted the accepted fact that periductal sepsis is common in younger women and discharge more likely in those over 40 years of age, but there is an overlap, especially with nipple discharge. All I stated – in company with others[4] – is that in some younger women there is a place for conservative duct excision. For obvious widespread duct disease total excision is indicated (sections 4 and 5 of the article).

My experience with microbiological cultures is less convincing than that of Mr Dixon. I have used flucloxacillin and metronidazole, also various cephalosporins and erythromycin, in patients who were sensitive to penicillins. I would be reluctant to reject metronidazole. Used alone in possible minor inflammatory breast situations, it has coincided with excellent and rapid resolution.

Regarding his comments on practical points.

(1) For non-lactating breast abscesses I am less conservative than Mr Dixon and confess to being heavily influenced by the teaching of G. J. Hadfield; I have found it eminently sound and sensible. Over a lifetime of surgical experience with breast disease, his messages appear unchanged[1,3,5].

Even with adequate drainage and liberal antibiotics I have needed to re-explore and drain further abscesses. A few have been associated with florid granulomatous disease (much more than lobulitis), but other patients have shown no such tissue changes.

(2) I am sceptical of Mr Dixon's assertions, and surgeons will have to decide from their own experience.

(3) I did not intend to indicate from sections 4 and 5 of the article that total duct excision should not be performed in younger women. I apologize if I caused a misunderstanding. Mr Dixon's good results from total duct excision, contrasting with the results quoted from Bristol[6], may possibly relate to case selection. However, experience since then and from referred patients still leads me to express caution. Hadfield[5], in 1990, highlights the complexity of recurrent periareolar sepsis and sets in perspective his use of antibiotics. I suspect that this surgical problem is under-reported. Our patients underwent mastectomy over 10 years ago and I know of one other patient since then in whom mastectomy should have been advised as disease was so extensive and the clinical course protracted.

(4) Regarding the surgical technique, I refer Mr Dixon to the original descriptions by Hadfield[3,7] and Urban[8]. The latter advocates far more breast excision than the former. Hadfield[3] recommends ligating the larger breast ducts emerging from the breast tissue with fine catgut. I have tended to excise a shallow disc of breast tissue with the ducts to ensure complete clearance. Herewith residual ducts cannot be ligated, and the logical procedure is 'underpinning' on the breast surface. I have no problem with 'pouting the papilla' but it must be done without damaging the blood supply. The so-called 'dead space' is difficult.

The infolding manoeuvre reported by Preece[9] is sometimes possible but may distort the nipple.

The current optimal method for mammary duct sepsis and fistula formation is included in section 7 of the article.

(5) A 'tender para-areolar cyst' is a discrete breast swelling within or around (in the average breast) a 5-cm circle centred on the papilla. In my experience it is a distinct entity, but a tender cyst may also arise elsewhere in the breast. Fine-needle aspiration cytology yields turbid fluid but not pus. The cytology shows many polymorphs, foamy histiocytes, 'round' cells and atypical cyst-lining cells, commonly apocrine in type. It is an important source of reported cytological atypia.

I was surprised that Mr Dixon, in his report with others on breast cyst morphology[10], did not include 'inflammatory' cysts. They differ from the simple apocrine variety.

The association of smoking and periductal inflammation I have mentioned. In those aged over 40 years, I suspect that symptomatic nodularity and nipple discharge is more likely in cigarette smokers, but my data are immature.

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Book reviews

Surgical Critical Care

J. A. Weigelt and F. R. Lewis Jr (eds). 285 × 220 mm. Pp. 458. Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £70.

This book is quite unique in that almost all the contributors are surgeons or surgical intensivists and the editors' objective is to provide the reader with a surgeon's perspective relative to critical care. The authors are predominantly American leaders who have made pioneering contributions in clinical or scientific aspects of critical care. The book comprises four sections and 27 chapters. The sections cover the specialty of surgical critical care, the assessment of the physiology of critical illness, management principles and techniques, and specific organ responses.

The role of the surgeon in the management of the critically ill patient has been eroded in recent times. Nevertheless, it is essential for surgeons with their unique perspectives to continue their involvement in critical care and in the multispecialty debates that are integral to it. Recognition of this need is also reflected by many regions in the UK incorporating modules of intensive care unit attachments in to basic specialist training. This book is thus a valuable resource for the interested surgeon and trainee as it is very informative on wide-ranging aspects of critical illness. A minor reservation is that there are few references from after 1994 and so some of the science may quickly become outdated in such a dynamic discipline. The essential principles and philosophies will hold, however, for the foreseeable future and this minor fault should not diminish its value. This is an excellent book and I would recommend it at least as a valuable resource in a surgical departmental library.

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Surgery of the Chest. 6th ed.

J. A. Waldhausen, W. S. Pierce and D. B. Campbell (eds). 240 × 197 mm. Pp. 656. Illustrated. 1995. St Louis, Missouri: Mosby-Year Book. £91.50.

This book provides a simple yet relatively comprehensive overview of cardiothoracic surgical techniques. It is well illustrated, with text and easily understandable sketches and diagrams on facing pages. Half of the book addresses thoracic surgery and half cardiac. It is written in a fairly didactic fashion and is, therefore, well suited to trainees entering the specialty. The thoracic surgery section covers surgically related physiology, basic diagnostic procedures, incisions and all the common thoracic operations, including pulmonary resections and a variety of oesophageal procedures. Of particular relevance, this section specifically addresses the newer techniques of video-assisted thoracic surgery, which distinguishes it from other general cardiothoracic textbooks. The cardiac section covers the surgical aspects of cardiopulmonary bypass and other cardiac assist devices, including the intra-aortic balloon pump and pacing systems. Acquired heart disease is covered well and, in particular, the emerging area of mitral valve repair is clearly illustrated. Surgery for congenital heart disease reflects the important shift in practice such that most lesions are now fully corrected surgically. More emphasis on myocardial preservation, which is essential to most cardiac procedures, would be useful, as there is so much international variation in technique. Writing a comprehensive book of this nature is difficult, but the authors have succeeded in producing a well balanced volume which I will be highly recommending to junior and middle-grade trainees in this specialty.

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MCQ Tutor for Principles and Practice of Surgery

T. Diamond and W. D. B. Clements. 215 × 137 mm. Pp. 228. Not illustrated. 1995. Edinburgh: Churchill Livingstone. £10.

As its title suggests, these MCQs are intended to accompany the book of the same name. They do this very successfully, but also usefully stand alone as a stimulus to further reading and as a simple way of revising. The 300 questions in this pocket-sized book are divided into 30 sections which cover a wide range of general surgery. I enjoyed trying to answer the questions, but found myself wanting to be asked a greater number of questions within each section. The reader should be immediately comfortable with the book's layout and should find it easy to use, although some of the questions suffer from the minor ambiguities which will be familiar to all those who have experienced MCQs before. Worthwhile explanations accompany many of the answers. There are few books of its kind around and it is not likely to be out of date for many years. The *Tutor* would particularly suit all levels of surgical trainee and senior medical students.

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Surgical Oncology. Companion Series to Bailey and Love's Short Practice of Surgery

T. G. Allen-Mersh (ed). 271 × 213 mm. Pp. 459. Illustrated. 1995. London: Chapman and Hall. £29.

I found this book very interesting, well written and well illustrated, but I was unsure at whom it was aimed. If it is aimed at the medical student, it is too long and too detailed; the same would apply to the general medical reader. If it is aimed at the surgical trainee, it is not detailed enough and would need more operative detail. But I was very pleased to read the section on the quality of life. Too often oncologists, including surgical oncologists, yield to patient or family pressure to 'do something' when he or she knows that anything that is done will make the quality of life poorer for the patient. The breast-care nurse (page 360) has a special place to play in helping the patient with breast cancer to cope with the implications of the disease. I think there is a similar need for patients with cancer of other areas and I was disappointed to find no mention of lung cancer. I know that there is a dispute about whether surgical oncology exists at all, but the editor must think it does and so the omission of this common cancer, often treated surgically, is surprising. Nevertheless, on the whole I found this a good book and one that will be useful to have on the shelves of any general surgical unit.

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Colorectal Cancer

N. S. Williams (ed). 252 × 193 mm. Pp. 187. Illustrated. 1995. Edinburgh: Churchill Livingstone. £49.50.

I read this book just after I had been asked to produce guidelines on the management of colorectal cancer for our hospital trust. The editor has succeeded admirably in bringing together the major recent developments in the subject in a small and easily readable volume. For the busy surgeon this is just the sort of publication which is of real practical value, both for the development of management policy and for higher surgical training in coloproctology. Contributions cover a wide range of topics: molecular biology and genetics of colorectal cancer, early diagnosis and screening, the management of polyps, surgical procedures (including endoscopy and laparoscopy techniques), and radiotherapy and chemotherapy. Sections including staging, surveillance and recurrence, and the treatment of liver metastases. The subject matter is covered in appropriate depth for practical colorectal surgeons. Each chapter is well referenced for further reading and illustrations are clear and effective. There is an international group of contributors drawn from many centres of excellence. This is a volume which can be strongly recommended.

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British Journal of Surgery 1996, 83, 1022

Notices and announcements

13–14 July 1996
Hong Kong Surgical Forum – Summer 1996
Hong Kong
Information: Forum Secretary, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

4–8 September 1996
International Congress of Phlebology
Corfu, Greece
Information: Professor P. Balas, 4 Hiraclitou Street, Athens 10673, Greece

6–8 September 1996
6th National Conference of the Indian Association of Surgical Gastroenterology
New Delhi, India
Information: Professor T. K. Chattopadhyay, Secretary, IASG, Department of Surgery, All India Institute of Medical Sciences, New Delhi 110029, India

8–12 September 1996
Annual Meeting and Postgraduate Course of the Cardiovascular and Interventional Radiological Society of Europe
Funchal, Madeira
Information: CIRSE 96, Pilatusstrasse 14, CH-8032 Zurich, Switzerland

9–11 September 1996
Basic Surgical Skills Workshop
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

11 September 1996
European Board of Surgery (Qualification in Vascular Surgery Assessments)
Venicer, Italy
Information: J. Buth, Secretary of the Division of Vascular Surgery and the European Board of Vascular Surgery, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, The Netherlands

18–19 September 1996
Fundamental Techniques of Plastic Surgery
Swansea, UK
Information: British Association of Plastic Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–20 September 1996
Society for Minimally Invasive Therapy 8th International Meeting
Milan, Italy
Information: G. Carminati, Istituto di Urologia, Universita degli Studi, Via della Commenda 15, 20122 Milan, Italy

19–21 September 1996
International Meeting on Inflammatory Bowel Disease
Capri, Italy
Information: Professor R. Caprilli, Cattedra di Gastroenterologia, Università de L'Aquila, Via S. Sisto 22E, 67100 L'Aquila, Italy

27–28 September 1996
Advanced Minimal Access Surgery for Theatre Personnel
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

3–4 and 9 October 1996
Laparoscopic Rectopexy
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

6–11 October 1996
Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: Nancy Sutton, Convention and Meetings Division, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-9424, USA

11 October 1996
Vascular Surgery – is it worthwhile?
Newcastle, UK
Information: Mr J. Chamberlain, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

13–19 October 1996
Recent Advances in Surgery of the Liver, Pancreas and Biliary System
Edinburgh, UK
Information: International Seminars Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16–18 October 1996
1st International Congress of the European Club for Pediatric Burns – Current Concepts in Pediatric Burn Care
Zurich, Switzerland
Information: M. Meuli, Director Pediatric Burn Center, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

19–24 October 1996
1st World Congress of Surgical Endoscopy
Beijing, China
Information: J. M. Phillips, General Chairman, 1st World Congress of Surgical Endoscopy, 13021 East Florence Avenue, Santa Fe Springs, California 90670-8774, USA

21–23 October 1996
4th Postgraduate Course in Surgery
Bangkok, Thailand
Information: V. Sachakul, Secretary General, Local Organizing Committee, Department of Surgery, Pramongkutklao Hospital, 315 Rajvithi Road, Bangkok 10400, Thailand

24–26 October 1996
4th European Conference on General Thoracic Surgery
Cordoba, Spain
Information: Dr F. J. L. Pujol, C/.Caño, 3-1.°, 1, 14001 Cordoba, Spain

27–30 October 1996
8th Overseas Meeting of the Royal College of Surgeons of Edinburgh jointly with the College of Surgeons of Hong Kong
Hong Kong
Information: The Clerk to the College, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

13–16 November 1996
3rd Hong Kong International Cancer Congress and the 7th Epstein–Barr Virus and Associated Diseases Congress
Hong Kong
Information: HKICC Secretariat, 2/F., Professorial Block, Queen Mary Hospital, Hong Kong

14–17 November 1996
3rd Congress of the International Association of Gerontology. European Region – Clinical Section
Thessaloniki, Greece
Information: Athos City Congress, 5 Agias Sofias Street, Thessaloniki 54623, Greece

18–22 November 1996
Hong Kong International Cancer Congress 1996
Hong Kong
Information: Gloria Wong, Cancer Center, Faculty of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

2–5 March 1997
11th Biennial Congress of the Asian Surgical Association
Hong Kong
Information: Congress Secretariat, ASA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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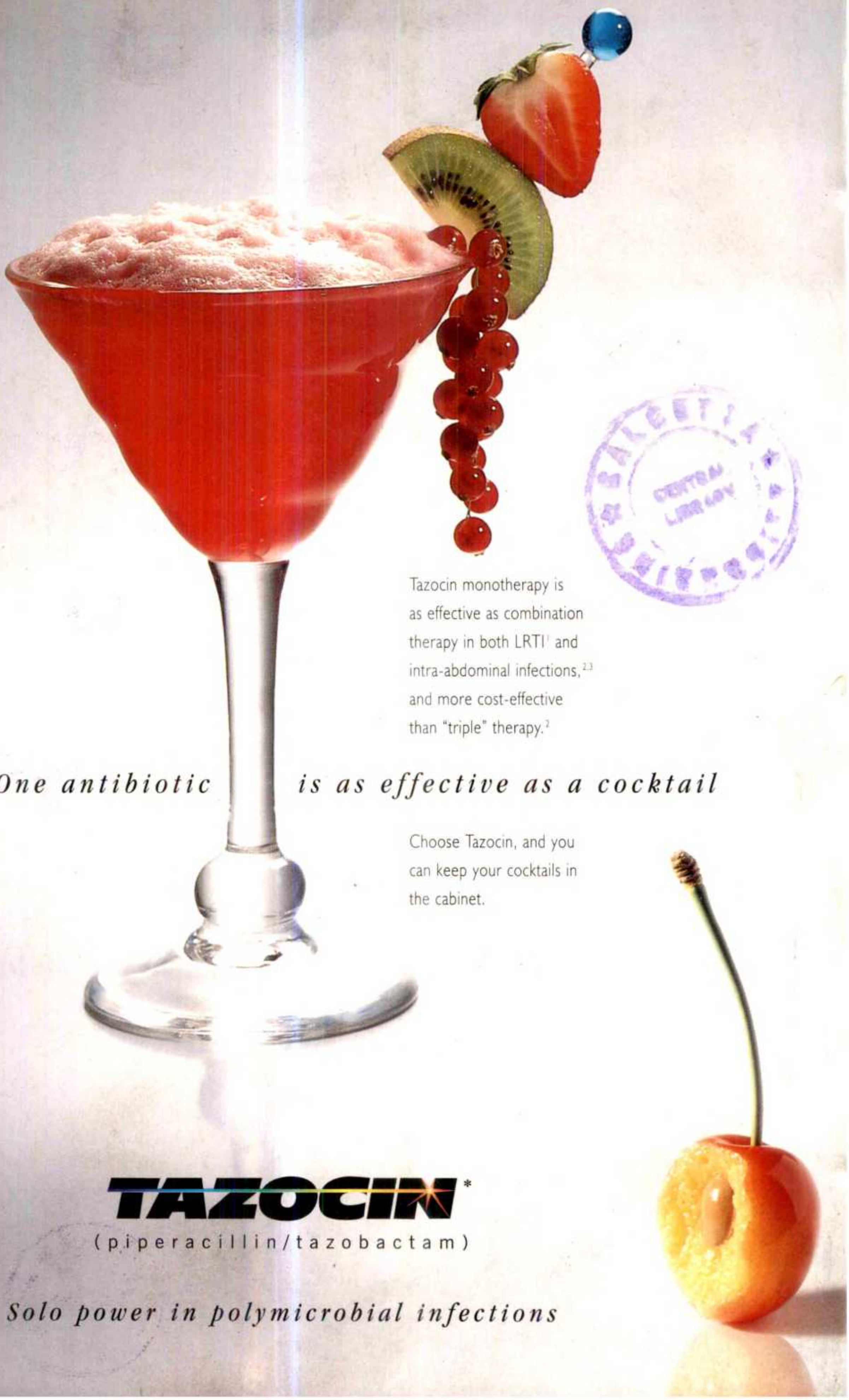

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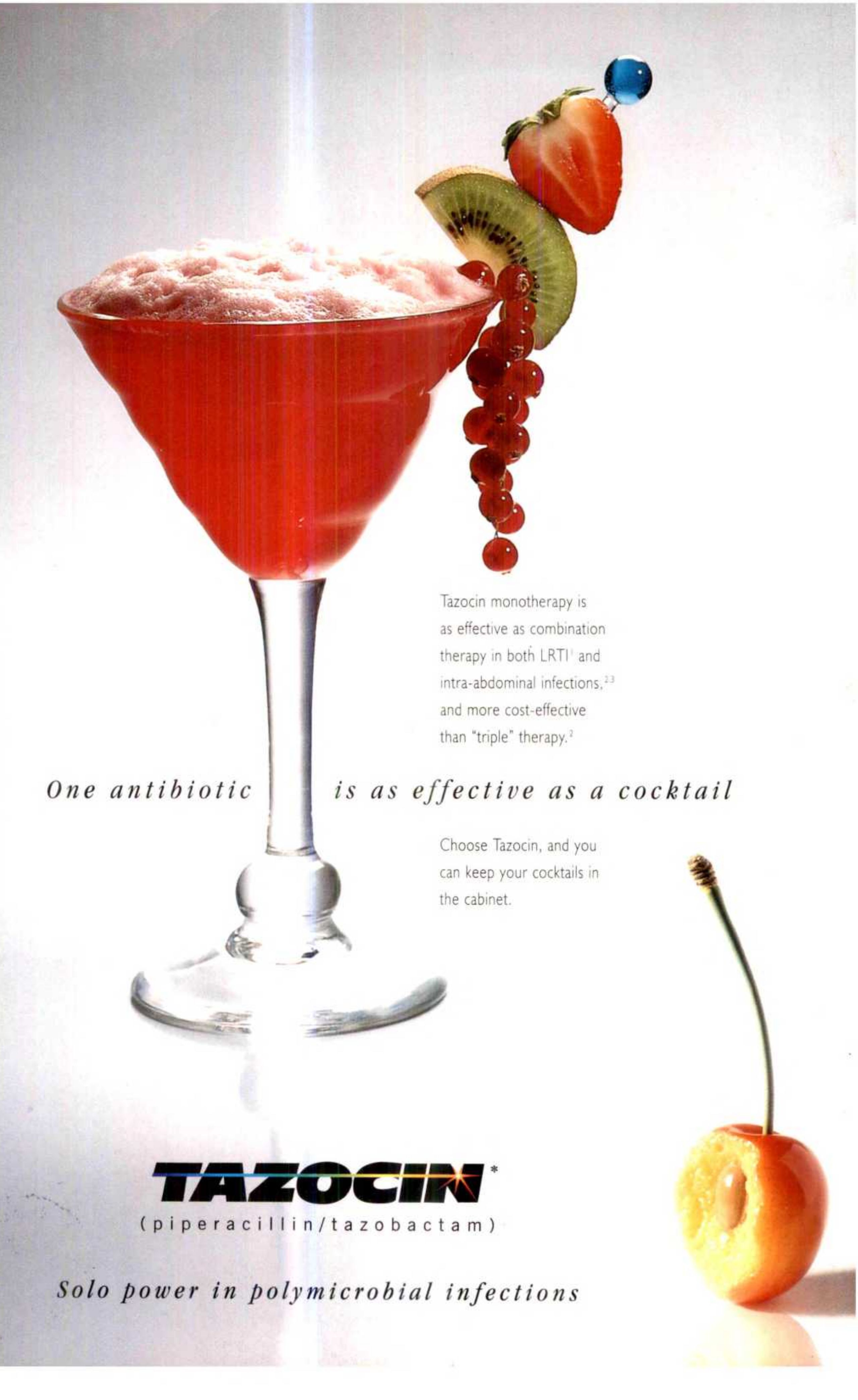

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ISSN 0007-1323

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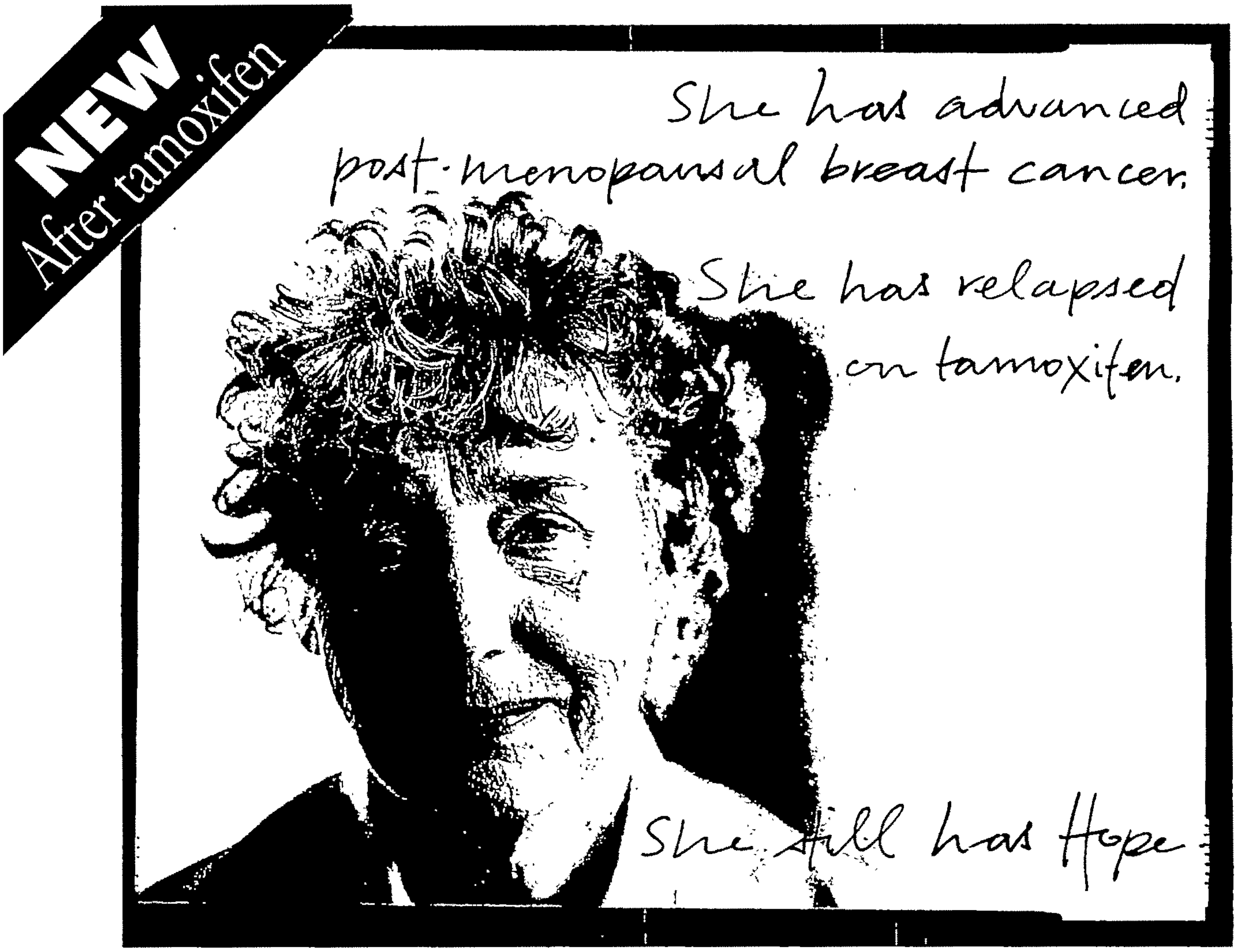
Printed by The Friary Press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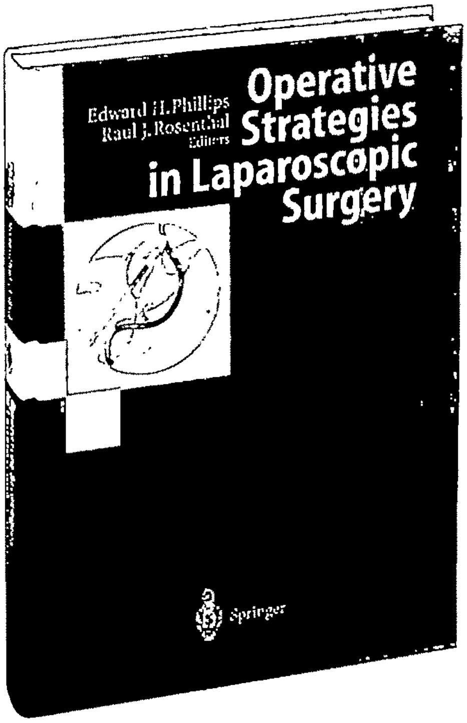

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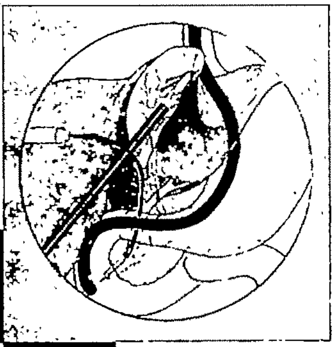

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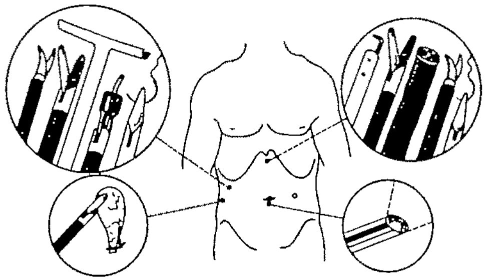

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THE AUSTRALIAN AND NEW ZEALAND JOURNAL OF SURGERY

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Editor in Chief
G. J. A. Clunie

ISSN 0004-8682
Published monthly

Editors
J. Ludbrook
I. B. Faris

The Australian and New Zealand Journal of Surgery, established for over 60 years, is the leading surgical journal published in Australia, New Zealand and the Asia-Pacific region. Published on behalf of the Royal Australasian College of Surgeons, the journal promotes outstanding surgical practice and research of contemporary and international interest.

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The Australian and New Zealand Journal of Surgery is published monthly. The subscription rates for 1995 (Volume 65) Aus$276.00 (Australasia), US$392.00 and Aus$560.00 (elsewhere). The Journal is dispatched to subscribers outside Australasia by surface air-lifted post.

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British Journal of Surgery 1996, **83**, 1025–1027

Leading articles

Saphenous vein stripping and quality of outcome

Prospective randomized studies, when well carried out, strongly influence subsequent practice. This was seen when the prospective trials of carotid endarterectomy *versus* best medical care were published. For many, such studies confirmed the obvious and verified well done retrospective observations which could have been the basis of guidelines for treatment. At present, the surgery of varicose vein disorders finds itself in an unenviable position with alternative forms of treatment being advocated. Many published observations on these treatments are available, yet no consensus has been reached. As it is unlikely that prospective randomized trials of varicose vein surgery will command financing comparable to that of the carotid trials, it is perhaps profitable to examine existing information as a guide to best practice.

Retrospective reviews of surgical experience are looked on with disfavour today; yet a thread of wisdom may be found in some such studies. Lofgren and colleagues[1] examined limbs of patients up to 5 years after high saphenous ligation or complete ankle-to-groin stripping and found 94 per cent excellent or good results after stripping compared with 40 per cent after high tie. This and other studies were dismissed by Woodyer *et al.*[2] as they presented their own prospective, randomized study. These authors compared saphenous vein stripping and stab avulsion with saphenous high tie and midthigh perforator interruption, finding no differences in either patient or physician evaluation at 3 years[2]. Results of this study were criticized because evaluation was entirely subjective[3].

There are now available six prospective studies in addition to that of Dormandy's group[2] comparing stripping of the saphenous vein with high ligation[3–9]. The Middlesex group[3], in a prospective randomized study, used duplex scanning for postoperative examination of valvular incompetence and photoplethysmography as an overall measure of venous function. 'Both objective tests of venous function and subjective assessment suggest that the results 21 months after surgery ... are improved by ... long saphenous vein stripping from groin to calf'. At Maastricht[4], stripping and ligation were prospectively randomized. Physician and patient assessment of results at 3 years was supplemented by Doppler ultrasonographic examination with the conclusion that '... the results remained significantly better for the stripping group ...'.

In Copenhagen, Jakobsen's prospective evaluation[5] (confirmed by Carl Arnoldi) concluded that saphenous varices are best treated by radical operation (stripping compared with high tie) in spite of the period of disability being significantly longer. In the New Zealand trial, each patient served as his own control, and evaluation was by a single observer at intervals up to 3–5 years after operation[6]. Results, judged only by the incidence of varicosities, '... were significantly better in limbs from which the long saphenous vein had been stripped. However, saphenous nerve paraesthesias biased patient evaluation against ankle-to-groin stripping'. At Lund, conventional subjective and objective evaluation was supplemented by foot volumetry before and after treatment[7]. The authors concluded that 'this study clearly supports the conclusion that CST (compression sclerotherapy) alone or in combination with high tie cannot replace radical surgery (saphenous stripping, perforator interruption and stab avulsion) for varicose vein disease with saphenous incompetence'.

Only the study of Hammarsten and co-workers[8] concluded '... that the removal of the long saphenous vein *per se* is of no therapeutic value if all perforators have been ligated'. However, as they emphasized in a later letter[9], only 'by means of a thorough (ascending and descending) phlebographic mapping of the insufficient perforators ... was precise perforator ligation possible'. In commenting on this, Darke[10] suggested that with regard to elimination of perforator-induced saphenous recurrences '... the simplest and least costly and uncomplicated way of eradicating the problem is to remove the saphenous trunk along with the existing and potentially incompetent perforators'.

The fate of the long saphenous vein after proximal ligation has been defined by duplex scanning. Evaluation by Rutherford *et al.*[11] showed that only 8–10 cm of proximal saphenous vein was obliterated after high ligation and all residual saphenous veins were patent. Friedell and colleagues[12] studied patients in Florida at a mean follow-up of 10 months and found 78 per cent of saphenous veins completely patent, 15 per cent with less than 10 cm obliterated and only 7 per cent with a greater length obliterated. In Cardiff[13], 75 limbs were assessed by duplex scan at a mean follow-up of 1 year. In 49 limbs (65 per cent) the entire saphenous vein was patent from ankle to groin and, in two additional limbs, less than 5 cm was lost proximally[13]. In a physiological evaluation of high saphenous ligation by duplex scanning and photoplethysmography, the Middlesex group found persistent reflux in 24 of 52 limbs with successful proximal ligation[14]. 'A satisfactory outcome was associated with absence of reflux down the long saphenous vein after operation' concluded the authors, who added that '... this operation fails to control functionally significant reflux within the long saphenous vein in a high proportion of cases'.

Some lessons can be learned from studies of recurrent varicose veins. Using duplex venous imaging and a careful search for sources of reflux, Thibault and Lewis[15] examined 122 limbs with recurrent varicose veins. Of these, 71 per cent had recurrent incompetent superficial thigh veins in the long saphenous distribution. Other findings regarding the short saphenous system are not relevant to the present discussion. Redwood and Lambert[16] studied 127 limbs with recurrent varicose veins and found that, when a single site of reflux was present, it was at the saphenofemoral junction in 58 per cent of limbs. They concluded that 'the high recurrence rate from the groin emphasizes the need for meticulous dissection around the saphenofemoral junction at the time of the initial surgery'[16].

Patterns of incompetence in 100 limbs with recurrent varicose veins were studied by duplex ultrasonography in Adelaide, Australia[17]. Saphenofemoral or recurrent groin tributary incompetence was present in 44 limbs and an incompetent long saphenous remnant in 20. The authors stated that 'the high incidence of long saphenous remnant incompetence in which no other site of incompetence was detected ... supports the argument for stripping'.

Ruckley's group studied 128 limbs with recurrent varicose veins by varicography and provided a useful classification of recurrent varices: a type 1 recurrence required re-exploration of the groin while a type 2 recurrence allowed operation to be performed without groin re-exploration[18]. In 75 of 128 limbs the long saphenous vein was present in the thigh and in 37 it was present to groin level. In all but 24 instances the site of recurrence could have been dealt with by a more complete primary procedure. A further important observation deriving from this paper is that saphenofemoral tributaries must be removed beyond their primary or even secondary tributaries to avoid leaving behind a network of collaterals, which can defeat the purpose of the primary operation. Ruckley and colleagues conclude 'it is clear from this and previous work that a large number of patients are undergoing inadequate first-time varicose vein surgery. The importance of accurately identifying and ligating the saphenofemoral venous complex, of obliterating all tributaries back to the secondary tributary points, and of stripping the long saphenous vein in the thigh and preventing recurrent varices must be emphasized yet again'[19].

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British Journal of Surgery 1996, 83, 1028–1030

Conjoined twins

The earliest record of conjoined twins in the English literature is of the Biddenden maids, May and Eliza Chulkhurst, who were born in Kent in 1100 and survived to the age of 34 years. The first successful separation of conjoined twins was documented in 1689 by Konig who was a mere spectator at the procedure performed by Johannes Fatio[1]. The most renowned twins were Chang and Eng Bunker, born in Siam (hence the popular term Siamese twins) in 1811. They were united by a short band at the umbilicus which eventually stretched to allow them to stand alongside each other. They were taken to the USA for exhibition, married sisters, had 19 children and died aged 63 years. By 1990, there were over 600 publications on conjoined twins and 167 attempts at separation[2].

The incidence of conjoined twins is estimated at 1 in 50 000 but, as around 60 per cent are stillborn, the true incidence is 1 in 200 000 live births. Girls predominate with a ratio of 3 : 1. Although it is generally accepted that the twins develop from a single fertilized ovum that fails to undergo complete division of the embryonic disc around the 15th–17th day of gestation[3], some have contested this fission theory and propose fusion of developing parts as the embryological basis for the condition[4].

Prenatal ultrasonography is capable of diagnosing a conjoined twin pregnancy as early as 12 weeks' gestation. Detailed scanning at around 20 weeks' gestation will define with reasonable accuracy the extent of the conjoined area and provide an assessment of which viscera are shared. This is of particular importance in relation to the heart, as twins with a shared heart have an extremely poor prognosis and termination of the pregnancy is invariably recommended. Computed tomography (CT) and magnetic resonance imaging (MRI) have been performed antenatally but, once the decision has been made to proceed with the pregnancy, these investigations can be carried out with greater accuracy after delivery. An additional advantage of prenatal diagnosis is that the time, place and mode of delivery can be planned[5]. In most instances, elective Caesarean section is the preferred option.

Early postnatal management after initial resuscitation consists of stabilization followed by maintenance of an adequate nutritional intake. During this period, which may extend for 4–6 months, detailed investigations are carried out to determine the precise anatomy of the union and to define any associated anomalies, in particular cardiac malformations. The range of investigations is determined by the site of the join and may include plain and contrast radiography, ultrasonography, echocardiography, CT and MRI with intravenous enhancement, radionuclide scanning and angiography. A single QRS complex on electrocardiography is an ominous sign of cardiac fusion.

The twins are classified according to the most prominent site of connection, plus the Greek term for fixed, 'pagos'. Thoracopagus is the most common variety, accounting for 40 per cent of reported cases, followed by omphalopagus (33 per cent), pyopagus (sacrum/buttocks) (19 per cent), ischiopagus (pelvis) (6 per cent) and craniopagus (2 per cent).

Once the anatomy of union has been determined accurately, plans are made for separation if this is considered to be a viable option. Where it is anticipated that there will be large areas devoid of skin after separation, additional skin for cover may be provided before operation using subcutaneous or intraperitoneal tissue expanders[6,7], artificial pneumoperitoneum or by preparing autologous cultured keratinocytes to cover granulating surfaces[8]. When only one twin is expected to survive, wide incisions on to the non-viable twin should provide sufficient tissue for primary closure of any defect. Prosthetic materials, such as polypropylene mesh, have been used when there is no alternative, but they are prone to infection and wound disruption. It is important to involve specialist colleagues, such as cardiac, orthopaedic and plastic surgeons and urologists at an early stage in the planning process. Before the procedure, it is useful to hold planning conferences to define responsibilities. The hospital press liaison officer should be kept informed of progress but no information need be released until separation has been achieved.

Anaesthesia involves two completely separate teams; all members should be clearly aware for which twin they are responsible. All drugs and intravenous fluids are calculated on a total weight basis with half being delivered to each twin. Because of the cross-circulation, drugs given intravenously may have an unpredictable effect and particular care must be taken to administer agents such as opioids incrementally. Endotracheal intubation should be via the nose for added security, especially when separation has been achieved and the infants moved to individual theatres, and for postoperative continuation of respiratory support. Full arterial and central venous monitoring is essential, with electrocardiography, pulse oximetry, capnography and recording of urinary output. Regular blood gas analysis is undertaken during the procedure and multiple venous access is crucial, as brisk haemorrhage may occur. Cardiovascular monitoring is particularly important since, with relative changes in position of the two infants, significant shifts in blood volume may develop[9].

Technical details of the operative procedure will be dictated by the anatomy of union, and by the organs and structures shared. In thoracopagus, the liver is invariably shared. In 90 per cent of cases there is a common pericardial sac which can usually be divided, leaving sufficient tissue to reconstruct a pericardium for each twin. Major myocardial connections are present in 75 per cent and only a few attempts have been made at separation with sacrifice of one twin; no long-term survivors have yet been reported. The upper gastrointestinal tract is common in 50 per cent of cases converging in the distal ileum, with a shared biliary system in 25 per cent. In omphalopagus, the liver is shared in 80 per cent and in 33 per cent the intestines join at the level of Meckel's diverticulum; the common terminal ileum and colon have a dual blood supply. The lower intestinal tract is common in both pyopagus and ischiopagus, and the genitourinary tract is shared in 15 per cent of the former and 50 per cent of the latter. It is not uncommon for the ureters in these situations to cross over from one twin and enter the contralateral bladder. The high mortality rate associated with craniopagus is almost entirely due to cerebral fusion which also contributes to neurodevelopmental sequelae in survivors.

Blood loss may be a major intraoperative problem, especially where there is pelvic bony fusion. Blood loss occurring during division of the liver may be minimized by using ultrasonic dissection, meticulously ligating major connecting vessels and coagulating minor vessels. By applying fibrin glue to the raw surface, postoperative ooze of blood and leakage of bile may be prevented[7,8]. Despite every attempt to define as accurately as possible all anatomical connections before surgery, 'unexpected events' are frequently encountered during the operation. Examples include abnormal vascular communications, and previously unidentified intestinal and genitourinary anomalies.

After surgery, survivors are extremely fragile. All intraoperative monitoring must be continued into the postoperative period and, because of the prolonged duration of surgery, the infants should be electively paralysed and ventilated mechanically for a variable period of time. Meticulous attention to monitoring fluid and electrolyte balance is required, especially to avoid overhydration which may precipitate cardiovascular instability. Sepsis is a major cause of mortality and morbidity, and strict precautions must be exercised, particularly when large skin defects are present[10]. Late unexpected deaths following separation are, unfortunately, not infrequent[11].

During the past decade my colleagues and I have accumulated experience of ten sets of conjoined twins at Great Ormond Street Hospital, London. Three had complex fused hearts for which no surgery was offered and all succumbed within a few days of birth. There was one emergency operation in an attempt to salvage the surviving twin following a traumatic delivery. Planned separation was carried out in six cases, with survival of both twins in two instances and one twin in three instances. One of the non-surviving infants had associated anomalies incompatible with survival, two died from congenital cardiac defects and there were two late 'unexpected' deaths.

Surgical separation of conjoined twins is a major undertaking. It requires careful and meticulous planning, involving two completely separate and dedicated teams of specialists, nurses and ancillary staff. Previous experience in the management of conjoined twins is invaluable in achieving a successful outcome.

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British Journal of Surgery 1996, 83, 1031–1036

Review

Peritoneal defences and peritoneum-associated lymphoid tissue

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The peritoneum is mainly protected by the innate immune system. This consists of mechanical clearance of the peritoneal cavity, activation of complement, and the actions of polymorphonuclear neutrophils and macrophages. The specific immune system, which is mediated by the activity of lymphocytes, provides a secondary amplification system that may be of great importance for patients with intraperitoneal sepsis. This review provides an overview of the relevant innate immune mechanisms and explores the possible role of peritoneum-associated lymphoid tissue.

The peritoneum is more than just a mechanical covering that allows organs to glide over one another; it also contains a multilayered and complex defence system that protects its serosal surface (*Table 1*). As Janeway[1] has commented, body surfaces such as the peritoneum rely mainly on innate immune mechanisms and, in this context, the specific immune system has evolved as a secondary amplification system. It is now becoming evident that peritoneum-associated lymphoid tissue (PALT) enjoys an intriguing relationship with both innate immune mechanisms and the gut-associated lymphoid tissue (GALT) system.

Table 1 Peritoneal defences

Type	Description
Innate	Antibacterial activity of peritoneal fluid, complement–mediated Bacterial absorption via diaphragmatic stomas Phagocytosis by polymorphonuclear leucocytes and macrophages Abscess formation Natural killer cells
Specific	Milky spots, immunoglobulin A antibody production Influx of memory T lymphocytes

Diaphragmatic stomas

The peritoneum overlying the muscular portion of the diaphragm is interrupted by a large number of intercellular gaps (stomas) that lie between the lateral border of mesothelial cells[2]. The local absence of a basement membrane allows the stomas to communicate with the underlying terminal lymphatic lacunae. These lacunae contain valves and run parallel to the muscular fibres of the diaphragm. They drain to the main lymphatic ducts via mediastinal lymph nodes.

Mesothelial cell processes on the border of stomas contain contractile filaments (actin) which can regulate the pore size; peritonitis causes the stomas to increase in size. The rapid absorption of particulate matter by the stomas is demonstrated by the recovery of bacteria from the thoracic ducts of dogs within 6 min of intraperitoneal contamination[3]. Consistent with this is the finding at autopsy that the anterior mediastinal lymphatics of patients dying from peritonitis contain bacteria[4]. Conventional wisdom holds that the rapid absorption of bacteria and bacterial toxins via the diaphragmatic stomas is one of the reasons for the high mortality rate associated with untreated peritonitis.

Peritoneal fluid and complement

The normal peritoneal cavity contains less than 100 ml of serous fluid, which is essentially an ultrafiltrate of plasma with a protein concentration lower than 3 g/dl[5]. The antibacterial activity of peritoneal fluid is mediated by complement[6]. The complement system consists of approximately 20 serum proteins which function to control inflammation[7]. Defence of the abdominal cavity against major contamination is triggered by the anaphylatoxins C3a and C5a, which are released during the complement activation induced by products of bacteria and inflammation[8]. C3a and C5a stimulate chemotaxis of neutrophils, and degranulation of basophils and mast cells[7]. In patients with cirrhosis and ascites, the concentration of C3 has been found to be an independent predictor for the occurrence of spontaneous bacterial peritonitis[9].

Neutrophils and macrophages

The ability of the peritoneal cavity to generate polymorphonuclear leucocytes (PMNs) and macrophages is prodigious. Most of what is known about the biology of PMNs and macrophages has been based on cells harvested from the peritoneal cavity. For example, stimulation of the peritoneal cavity with thioglycollate results in the production of 'elicited' macrophages. Once elicited macrophages have been primed with interferon (IFN) γ they become activated, expressing high levels of major histocompatibility complex (MHC) class II molecules and displaying good effector mechanisms against microbes, such as *Leishmania* and *Candida*[7].

The peritoneum usually contains fewer than 300 cells per mm^3, mostly macrophages plus some desquamated mesothelial cells and lymphocytes. Abdominal surgery, even in the absence of gross contamination or infection, elicits a rapid and transient influx of PMNs which may raise their numbers[10] to more than 3000 per mm^3.

Paper accepted 22 February 1996

Following the PMN response the peritoneal cavity is invaded by macrophages. Degranulation of peritoneal mast cells releases vasoactive substances (increasing vascular permeability), complement (components of which are chemotactic for macrophages), and opsins, which coat bacteria and promote phagocytosis. In addition, soluble factors secreted by PMNs upregulate macrophage phagocytic functions within 6 h of bacterial contamination[10], all combining to maximize bacterial clearance from the peritoneum by macrophages.

Milky spots in the omentum

The omentum localizes infection by adhering to sites of inflammation or perforation. It contains an abundant supply of blood vessels, has potent angiogenic activity and is a rich source of growth factors. The omentum is the only site within the peritoneal cavity, other than the diaphragmatic stomas, that has the ability to absorb foreign particles and bacteria[11]. Aggregations of cells within the omentum, known as 'milky spots', are a source of PMNs, macrophages and lymphocytes. Milky spots composed of these mesenchymal cells are found surrounding capillary convolutions that have been termed 'omental glomeruli'[12–14]. They appear as tiny cotton-wool-like masses to the naked eye. Milky spots were first described in rabbit omentum by von Recklinghausen[15] in 1863 and were not documented in humans until 1921[16]. The number of milky spots is highest in infancy at 20–40 per cm^2, decreasing to approximately 5 per cm^2 with age[17]. Studies by Trebichavsky *et al.*[18] showed that the development of omental lymphatics in pigs is closely related to the general immunological status of the animal.

Beelen[12] studied milky spots in an unstimulated state in adults and found a cellular composition of about 70 per cent macrophages, 10 per cent B lymphocytes, 10 per cent T lymphocytes, and mast cells. B and T lymphocytes are clustered near the peritoneal surface of the milky spots and orientated toward the peritoneal cavity, ready for migration. During inflammation, the number and size of omental milky spots increases dramatically, and some develop germinal centres and produce antibodies, as demonstrated by the intraperitoneal administration of a killed streptococcal preparation which produced such changes within 3 h[17]. Milky spot lymphocytes are able to enter and exit the peritoneal cavity via the overlying mesothelial stomas[19]. Funda *et al*[20]. found that activation of milky spots in mice is not influenced by the athymic state. It appears that activation depends on a basic macrophage defence, which is well developed in the athymic model, and is self-regulated and shaped by a sequence of cell immigration, settling, differentiation and emigration.

The compartmentalization of lymphocytes

The lymphoid system is functionally compartmentalized into primary, secondary and tertiary lymphoid organs[21]. Primary lymphoid tissues include the bone marrow and thymus, and are responsible for the production of naive lymphocytes. Secondary lymphoid tissues, such as lymph nodes, the spleen and GALT, are specialized for the accumulation and presentation of antigen to both naive and memory lymphocyte subsets. The remainder of the body's tissues are considered tertiary lymphoid tissues, in that they normally contain only a few lymphoid elements, but can be induced to recruit lymphocytes during inflammation. Each lymphoid tissue is further subdivided into discrete microenvironments characterized by distinct types of lymphocytes and stromal cells. Lymphocyte homing is the physiological process by which lymphocytes seek out and localize to particular tissues and microenvironments. Homing mechanisms play a major role in the maintenance of these specialized microenvironments, and are critical for the dispersal and targeting of naive and memory lymphocyte populations that are required for effective immune surveillance.

Peritoneal lymphocytes

The periphery of the immune system, as opposed to the central lymphoid organs, contains non-homogeneously distributed B and T lymphocytes whose phenotype, repertoire, developmental origin and function are highly divergent[22]. Non-conventional lymphocytes bearing a phenotype that is rare in the blood, spleen or lymph nodes of undiseased individuals are encountered at high levels in tertiary lymphoid tissues (e.g. Ly1$^+$ or CD5$^+$ B cells in the peritoneum which are involved in B cell interactions). It appears that, in contrast to the bulk of T and B lymphocytes, certain $\gamma\delta$ and $\alpha\beta$ T lymphocytes found in the periphery, as well as most Ly1$^+$ B lymphocytes, do not depend on the thymus or bone marrow respectively for their development, but arise from different non-conventional lineages (i.e. extrathymic differentiation). In addition to divergent lineages that are targeted to different organs and guided by tissue-specific homing receptors, local induction or selection processes may be important in the diversification of peripheral lymphocyte compartments. Selection may be exerted by local antigens, cytokines, cell–matrix interactions and antigen-presenting cells, the function of which varies in each anatomical localization; this leads to the expansion and maintenance of some clones and to the dilution or deletion of others.

Extrathymic pathways of T lymphocyte differentiation have been demonstrated to occur in multiple sites in mice[23]. Such sites include the sinusoids of the liver, the intraepithelial region of the intestine and the omentum of the peritoneal cavity. Although these extrathymic pathways are minimal in the young, they become predominant with ageing. Extrathymically differentiated T cells display many properties distinct from those of intrathymically differentiated T cells, for instance double-negative CD4$^-$ CD8$^-$ cells (cells that express neither CD4 nor CD8), the expression of an $\alpha\alpha$ homodimer of CD8, self-reactive oligoclones, or constitutive expression of the interleukin (IL) 2 receptor β chain. Cumulative evidence reveals that the extrathymic pathways comprise a primitive and fundamental immune system in the body and play a pivotal role in immune reactions under conditions of ageing, malignancy, autoimmune disease, pregnancy and bacterial infection such as peritonitis.

Kasaian and Casali[24] have proposed that the human B lymphocyte repertoire includes at least three distinct B lymphocyte subsets: B-1a (Ly1$^+$ or CD5$^+$) cells, which develop from progenitors in the omentum[25] and are maintained in adult life by virtue of their self-replenishing nature; B-1b (Ly1$^-$ or CD5$^-$) cells, progenitors of which can be found in the splanchnic area and, perhaps, adult bone marrow; and finally B-2 (CD5$^-$ CD11b$^-$) cells, which arise in the fetal liver and are continuously replenished in adult life by progenitors in the bone

Table 2 Cell-determinant markers related to peritoneal defences[7]

Antigen	Function
CD4	MHC class II receptor on T lymphocytes
CD5	Marker of B cell differentiation
CD8	MHC class I receptor on T lymphocytes
CD11a	α chain of leucocyte functional antigen 1, facilitates binding of leucocytes to lymphocytes and endothelial cells
CD11b	α chain of complement receptor 3
CD14	Cell-surface protein that binds lipopolysaccharide
CD18	The β chain of CD11, facilitates binding of monocytes to leucocytes
CD29	The β chain of very late activation antigen, facilitates binding of lymphocytes to endothelial cells
CD54	Intercellular adhesion molecule 1, facilitates binding of endothelial cells to leucocytes

CD, cell determinant; MHC, major histocompatibility complex

marrow. The different B lymphocyte types are distinguished by their differential expression of surface CD5 (expressed by cells predisposed to autoantibody production[7]), the CD11b or Mac-1 adhesion molecule, CD14 (the lipopolysaccharide-binding protein (*Table 2*)), and the different classes and specificities of the immunoglobulins they produce[24].

Phenotypically Ly1$^+$ and Ly1$^-$ B lymphocytes are essentially identical, distinguished only by the presence or absence of the CD5 antigen. Both express CD11b and produce high levels of immunoglobulin (Ig) M, as measured in adoptive transfer experiments. These experiments involve the transfer of Ly1$^+$ and Ly1$^-$ B lymphocyte fractions into irradiated recipients to determine the ability of the cells to reconstitute the peritoneal population. Functionally no difference between the two populations has yet been identified; although Ly1$^+$ B lymphocytes may be more involved in regulation of B lymphocyte function and development[26], while Ly1$^-$ B lymphocytes are more involved in interactions between B and T lymphocytes[27].

Ly1$^+$ B lymphocytes have been reported to produce a number of different antibodies and autoantibodies[28]. Andrade and associates[29] found that the antibody repertoire expressed by peritoneal Ly1$^+$ B lymphocytes of adult mice is not the result of a genetic programme, but rather the consequence of local age-dependent cellular selection mechanisms. Further studies by Thomas-Vaslin and colleagues[30] found that the bulk of natural IgM secretion can be attributed to peritoneal Ly1$^+$ B lymphocytes and their progeny, and that this secretion is independent of adult bone marrow precursors. In addition, roughly half of the IgA plasma cells in the lamina propria of the gut are derived from the peritoneal B lymphocyte lineage, suggesting an important role for peritoneally derived B lymphocytes in the mucosal immune response[31,32].

McIntyre *et al.*[33] used *in situ* hybridization to study immunoglobulin messenger RNA (mRNA) levels in murine peritoneal and splenic B lymphocytes. Peritoneal Ly1$^+$ B lymphocytes were found to be mainly responsible for the production of intermediate immunoglobulin mRNA levels. The Ly1$^-$ B lymphocyte subpopulation contained a lower percentage of intermediate immunoglobulin mRNA-producing B lymphocytes. Peritoneal B-2 cells produced negligible levels of immunoglobulin mRNA, comparable to those of unfractionated splenic B lymphocytes. Northern analysis showed that the majority of immunoglobulin mRNA expressed in the peritoneum is of the membranous rather than the secreted form. Consistent with that result, in short-term culture peritoneal cells showed markedly less immunoglobulin secretion than did spleen cells. These studies emphasize that, within the peritoneal cavity, B lymphocytes do not tend to become antibody-secreting cells.

Cross-talk between lymphocytes and phagocytes

A complex relationship exists between cytokines, adhesion molecules and leucocytes, all of which participate in an adhesion cascade. Adult mammals respond to tissue damage by implementing the acute-phase response, which comprises a series of specific physiological reactions involving cytokines and adhesion molecules[35,36]. The result of this cascade of events is the emigration of leucocytes from the periphery to an inflammatory site, where the production of oxygen radicals, nitrogen radicals and proteases may lead to tissue injury.

Macrophages are able to modify their behaviour in response to diverse signals from other cells and the extracellular matrix[35]. Lymphocyte-derived cytokines, such as tumour necrosis factor α and IL-6, augment macrophage cytokine production during Gram-negative bacterial peritonitis[36]. In addition, following T lymphocyte immunity reactions, macrophages express high levels of MHC class II molecules and can be microbicidal[37], increasing their ability to clear infection.

Exposure to various pathogens can stimulate at least two patterns of cytokine production by T helper lymphocytes (CD4$^+$ T lymphocytes). Responses that result in secretion of IFN-γ, lymphotoxin and IL-2 are classified as T helper 1 (Th1); these cytokines induce activation and proliferation of lymphocytes and macrophages, and increase cellular adhesion[7,40]. CD4$^+$ T lymphocyte production of IL-4, IL-5, IL-9, IL-10 and IL-13 is called a T helper 2 (Th2) response, and stimulates proliferation of mononuclear cells and lymphocytes, mast cell growth and IL-6 production[41–43]. Differentiation of CD4$^+$ T lymphocytes into either Th1 or Th2 cells is influenced by the cytokine milieu in which the initial antigen priming occurs. Ferrick *et al.*[34] used flow cytometry to identify the presence of intracellular cytokines and analyse T lymphocyte production of IFN-γ and IL-4 from mice infected with *Listeria monocytogenes* or *Nippostrongylus brasiliensis*. They showed that γδ T lymphocytes discriminate early in infection between these two pathogens by producing cytokines associated with the appropriate T helper response.

Peritoneal immunocytes and gut-associated lymphoid tissue

The association between peritoneal lymphocytes and GALT is demonstrated by the induction of both systemic and mucosal immune responses following intraperitoneal immunization. Intraperitoneal priming results in a vigorous IgA antibody response within the gut when the same antigen is subsequently given enterically or systemically. In contrast, primary intraduodenal immunization results in a substantially lower IgA response[44,45]. This phenomenon was explained by Kroese *et al.*[31], who showed that B lymphocytes from the murine peritoneal cavity repopulated the intestinal lamina propria of recipient mice with IgA-secreting cells, indicating an important role for peritoneal B lymphocytes in the GALT system.

PALT is thought to induce a mucosal immune response in a variety of ways. Antigen may drain via lymphatics to lymph nodes, leading to a systemic response. Intraperitoneal immunization has also been shown to lead to the local response of resident B lymphocytes, resulting in the appearance of peritoneally derived antibody-secreting cells in GALT. Alternatively, stimulated lymphoblastoid B lymphocytes may leave the peritoneal cavity via the thoracic duct, enter the circulation and migrate to other mucosal tissues[46].

Peritoneal cells are found to migrate to the subcapsular sinus and medulla of the parathymic lymph node and paratracheal lymph node. Fluorescence-labelled antigen-presenting cells, such as granulocytes, macrophages and dendritic cells, are also present in the dome and B lymphocyte follicles of Peyer patches after intraperitoneal labelling. The presence of peritoneal antigen-presenting cells within the Peyer's patches – the antigen-sampling sites of the gut – indicates a role for these cells in the priming of mucosal lymphoid tissues[47]. Primed tissues mount a faster immune response to foreign particles and bacteria, possibly aiding in the prevention of bacterial translocation, the passage of viable bacteria across the epithelial mucosa into other tissues. Bacterial translocation is a serious complication in critically ill patients and may result in multiple organ failure.

Homing of effector cells to the peritoneum

Adhesion molecules such as selectins and integrins are known to mediate leucocyte attachment and transmigration through activated vascular endothelium. However, the molecules that mediate subsequent leucocyte entry into non-vascular spaces, such as the abdominal cavity during states of peritoneal inflammation, have not been identified. Because the peritoneal mesothelial lining represents the final barrier to leucocyte migration into the abdomen, it is likely that adhesion molecules expressed by mesothelial cells are involved in this process. Cannistra *et al.*[48] have developed an *in vitro* binding assay using confluent layers of normal human mesothelial cells to determine which adhesion molecules might be involved in T lymphocyte–mesothelial recognition. Interestingly, cultured human mesothelial cells were shown to express vascular cell adhesion molecule 1, which is a ligand for the $\alpha_4\beta_7$ adhesion molecule expressed by T lymphocytes (*Table 3*). Mesothelial cells were also noted to express intercellular adhesion molecule 1, CD29 and CD44, but not CD18 or endothelial leucocyte adhesion molecule 1.

Peritonitis

The peritoneum deals with infection in three ways. First, there is absorption of bacteria into the lymphatics via the stomas of the diaphragmatic peritoneum. Second, bacteria are phagocytosed by either macrophages or PMNs. Third, a number of factors act to localize the infection as an abscess[53]. The initial phase of peritonitis may contain a profound systemic component. Gram-negative aerobic bacteria release endotoxin which acts via mediators to initiate a systemic septic response[53]. There is a dramatic increase in the concentration of endotoxin in the portal vein within 10 min of peritoneal contamination[54].

Dunn *et al.*[55,56] have studied the clearance of bacteria from the peritoneal cavity using an animal model. They instilled radiolabelled dead *Escherichia coli* and found

Table 3 Adhesion molecules associated with the peritoneum[49–52]

Adhesion molecule	CD no.	Cells expressing adhesion molecule	Ligand	Cells expressing ligand
Endothelial leucocyte adhesion molecule 1	CD26E	Endothelial cells	E-selectin ligands	Granulocytes, monocytes, CD4$^+$ T lymphocytes
ICAM-1	CD54	B and T lymphocytes, endothelial cells, monocytes, dendritic cells, thymocytes, epithelial cells, keratinocytes, chondrocytes, fibroblasts, mesothelial cells	LFA-1 (CD11a/CD18) Mac-1 (CD11b/CD18)	Leucocytes Monocytes, NK cells, neutrophils
VCAM-1	CD106	Endothelial cells, macrophages, dendritic cells, bone marrow, fibroblasts, myoblasts, mesothelial cells	VLA-4 (CD29/CD49d) $\alpha_4\beta_7$	Myoblasts, thymocytes, lymphocytes, monocytes Lymphocytes
Mucosal addressin cell adhesion molecule 1	—	Mucosal lymphoid high endothelial venules	L-selectin	Lymphocytes, neutrophils, thymocytes, monocytes, eosinophils, basophils, NK cells
CD44/H-CAM/ GP-90 Hermes	CD44	B and T lymphocytes, monocytes, neutrophils, epithelial cells, fibroblasts, mesothelial cells	Hyaluronate, collagen	Endothelial cells, extracellular matrix
VLA-4	CD29/CD49d	Myoblasts, thymocytes, lymphocytes, monocytes, mesothelial cells	VCAM-1, fibronectin	Endothelial cells, macrophages, dendritic cells, bone marrow, fibroblasts, myoblasts
LFA-1	CD11a/CD18	Leucocytes	ICAM-1, ICAM-2, ICAM-3	B and T lymphocytes, monocytes, endothelial cells, granulocytes, dendritic cells, thymocytes, epithelial cells, keratinocytes, chondrocytes, fibroblasts

CD, cell determinant; ICAM, intercellular adhesion molecule; LFA, leucocyte functional antigen; NK, natural killer; VCAM, vascular cell adhesion molecule; VLA, very late activation antigen that one-half were mechanically cleared and one-third were engulfed by macrophages. Live *E. coli* were initially controlled by these mechanisms, but they then increased in number for up to 4 h before growth was curtailed by PMNs. The size of the neutrophil response was quantal, i.e. not related to the size of the inoculum.

Survival beyond the initial septic phase is characterized by either recovery or the localization of infection as abscesses[57]. Weinstein *et al.*[58] developed a rat model by implanting barium and faeces into the peritoneal cavity. They observed two phases in the response. During the first 5 days there was acute generalized peritonitis, prominently involving *E. coli* and enterococci, with a mortality rate of 40 per cent. After that, there was a more benign stage of multiple abscess formation involving predominantly *Bacillus fragilis*. It seems that unencapsulated *B. fragilis* needs the presence of aerobes before it can form an abscess, while encapsulated *B. fragilis* freely forms abscesses[59]. The capsule might be important by promoting adhesion to the peritoneal wall or inhibiting neutrophil phagocytosis.

Conclusion

Exposure of the peritoneum to antigens can result in specific lymphocyte-mediated responses. The omentum is the site for Ly1$^+$ or CD5$^+$ B lymphocyte differentiation, which are the cells responsible for supplying almost half of the IgA plasma cells found in the gut. This suggests a role for peritoneally derived B lymphocytes in the mucosal immune response. In patients with peritonitis the peritoneal lymphocytes cross-talk with effector cells and may play a crucial role in the localization of intraperitoneal abscesses.

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British Journal of Surgery 1996, 83, 1037–1046

Review

Endocrine and paracrine hormones in the promotion, progression and recurrence of breast cancer

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Both normal and neoplastic breast tissues are stimulated by endocrine and paracrine hormones. Epidemiological studies have demonstrated the significant role that hormones, growth factors and cytokines have in the promotion, progression and recurrence of breast cancer. Significant variations in the hormonal environment occur based on age, the cyclical changes occurring during the menstrual cycle and (mammographically determined) variations in breast composition. These variations have a significant influence on rates of local recurrence of breast cancer and survival. This review analyses data relevant to these issues and suggests means by which operative results may be improved.

The past decade has seen changing concepts in the surgical control and cure of breast cancer, and in the molecular biology of cancer initiation and tumour–host interaction. This review demonstrates that the endocrine and paracrine hormone profile of the breast at the time of cancer resection modulates the subsequent course of the disease, and provides some understanding of the biological plausibility of this phenomenon. It brings together concepts of breast proliferation and ties them in a common theme: that the same factors which cause normal breast tissue to proliferate during pubescent development and during the cyclical changes of the menstrual cycle are involved in the promotion, progression and recurrence of breast cancer. This interplay is intimately related to the age of the patient, the cellular composition of the breast and the hormonal milieu as governed by the menstrual cycle or by the exogenous administration of sex hormones. An understanding of the mechanisms involved in the proliferation and maturation of normal breast tissue yields some insight into the hormonal influences that govern many facets of early breast cancer.

Mechanisms involved in the proliferation of normal breast tissue

Normal female breast development

The capacity of normal breast tissue to develop depends on three major interrelated factors: age, composition of breast tissue and hormonal environment (both past and present). The teenage period after puberty is the most proliferative stage in which the lobules are developing. The lobules become almost fully developed by the age of 25, although some lobular proliferation persists until about 35 years of age[1]. Additionally, during each monthly cycle between menarche and menopause the ductal epithelium is renewed continuously by the cyclical menstrual hormones, although there is some decline in the epithelial turnover in later reproductive years[2]. The breast goes through many changes during the menstrual cycle: breast volume, fat to water ratio, lymph flow and temperature all vary as a result of hormonal changes. Childbirth with its postlactational involution tends to change the lobular structure to a more differentiated structure[3]. This results ultimately in a decrease in lobules without any significant changes in the ducts and connective tissue stroma. The major involution is associated with menopause. It includes a preclimacteric phase beginning at approximately 35 years of age, and a postmenopausal phase starting at menopause[4]. During this latter phase, the ductal and lobular epithelium, as well as the adjacent fibrous connective tissue stroma, regress and are each gradually replaced by adipose tissue. These involutional changes take place over 15–20 years and depend on the interaction between the breast epithelium and the fibroconnective stroma[1]. Clinically these changes produce the shrunken, pendulous breasts of the elderly, and result in very good mammographic visualization of the atrophied breast.

In the young premenopausal breast, approximately 15 per cent of volume consists of epithelial cells, whereas in the 60-year-old woman less than 5 per cent of the breast consists of epithelial cells[5]. In detailed analyses of mastectomy specimens, Anastassiades *et al.*[6] evaluated breast composition at different ages. In the 31–40-year age group, 54 per cent of breasts have a large amount of solid tissue (mammary parenchyma and fibrous stroma) while none are extremely fatty. In contrast, over 70 years of age fatty breasts comprise 46 per cent of the specimens and only 8 per cent have solid tissue (*Table 1*). Similar changes in composition with age have been confirmed by others[7]; these changes are explained at least partially by changing hormonal influences over time.

Hormonal influences in breast development and involution

In physiological amounts, oestrogen and, to a lesser extent, progesterone, are mitogenic to breast tissue. Changes in the levels of these steroid sex hormones during the menstrual cycle profoundly influence both the stroma and the epithelium[8]. In premenopausal women, the proliferative activity of breast tissue is maximal during the luteal phase of the menstrual cycle, when increased progesterone levels synergistically enhance the effects of

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Paper accepted 28 February 1996

Table 1 Relationship between age and breast composition

Age of patient (years)	Solid tissue* (%)	Fatty tissue (%)
31–40	54	0
41–50	17	8
51–60	10	7
61–70	4	11
>70	8	46

*Mammary parenchyma and fibrous stroma. Modified from Anastassiades *et al.*[6]

oestrogen[9]. The average epithelial proliferation during the luteal phase is reported to be 3–3·9 times greater than that during the follicular phase[10]. The peak in proliferative activity occurs in the mid-luteal phase[9,11], occurring on day 21 in the nulliparous and on day 25 in the parous woman[12]. The nadir of proliferative activity occurs during the second week of the follicular phase. Proliferative rates also correlate with age[9,13]. Younger individuals closer to menarche have a 2·5-fold higher proliferative activity compared with older women nearing menopause. Surprisingly, this does not correlate with oestrogen levels, which are higher among older (aged 28–40 years) than among younger (aged 18–23 years) women[14]. In postmenopausal women, epithelial proliferation rates are very low[10].

Normal homeostatic functioning of breast tissue during the menstrual cycle ensures epithelial cell turnover, alternating between cellular proliferation and programmed cell death (apoptosis). The balance between cell proliferation and cell death in the earlier reproductive years favours proliferation, as there is a progression of the cell population over each ovulatory cycle[15]. There is a common regulatory mechanism between mitosis and apoptosis, wherein apoptosis is regulated in a reciprocal relationship to mitosis by growth factors and trophic hormones[16–18]. The final outcome of a given cell cycle is dependent upon whether or not that cycle is supported by growth factors[19]. To maintain viability of a particular cell, at least one growth factor critical for this cell type must be available, otherwise the cell undergoes apoptosis[20]. The rate of apoptosis is maximal in the late luteal phase, approximately 3 days after the peak of proliferative activity. The least apoptosis occurs just before ovulation, when the oestrogen levels are highest[11].

Growth factor potential of breast stroma

In addition to patient age and hormonal environment, a third factor is the ability of breast stromal cells to accrue and secrete growth factors for any given hormone level. Oestrogen has the most important endocrine influence on the breast and appears to act by triggering production of locally acting hormones (i.e. growth factors)[21]. Growth factors are a group of specialized polypeptides secreted by platelets, inflammatory cells, endothelial cells, fibroblasts and epithelial cells. Growth factors represent a system of signals that organize and coordinate cellular proliferation; they may function either as growth stimulators or growth inhibitors. At basal levels they provide a homeostatic environment, but at raised levels they are responsible for the rapid cell divisions that characterize foetal development, wound healing and neoplastic proliferation[22]. For a growth factor to act on a cell, that cell must express the appropriate growth factor receptor. Growth factor activity is the local tissue mechanism of action of oestrogen and progesterone. While this activity has been studied in human mammary tissue only in the context of malignant epithelial cells, it is almost certainly crucial also to the regulation of the normal mammary epithelium[23].

In hormone-responsive breast cancer cells, oestrogen controls mammary proliferation through upregulation of stimulatory growth factors (transforming growth factor (TGF) α, insulin-like growth factor (IGF) 2 and amphiregulin) and growth factor receptors (epidermal growth factor (EGF) and IGF-1 receptors), and downregulation of inhibitory growth factors (TGF-β)[23]. Analogous effects have been observed with progestins[23]. The most important mitogenic factors for mammary cells are members of the EGF family (EGF, TGF-α and amphiregulin)[24], each of which interacts with the same growth factor receptor (EGF receptor). Oestrogen and progesterone act on mammary epithelial cells to induce synthesis and secretion of additional growth factors. These growth factors may interact with receptors on nearby cells, enter the general circulation and exert distant effects, or adhere to extracellular matrix molecules[24]. Cells deprived of these growth-promoting agents have a reduced proliferative rate, enter a G0 quiescent phase of the cell cycle or undergo apoptosis.

In the breast, the stroma and epithelium intercommunicate with each other through these growth factors in so-called paracrine loops. This communication is critical for breast development and proliferation[25]. Stromal growth factors (EGF, TGF, IGF-1 and IGF-2) can modulate epithelial cell proliferation, and epithelial growth factors in turn can modulate stromal (i.e. fibroblastic and angiogenic) proliferation[25]. In *in vitro* studies, oestrogen-induced proliferation of mammary epithelial cells is seen only when they are co-cultured with mammary stromal cells[26]. In the absence of such stromal cells, no epithelial cell proliferation occurs; conversely, in the absence of epithelial cells stromal cells do not respond to oestrogen. These bidirectional fibroblast–epithelial cell interactions are required for growth responses to oestrogen[25]. Similarly, an *in vivo* study in humans has demonstrated that production of the mitogenic growth factor for stromal cells, platelet-derived growth factor (PDGF), is restricted to benign and malignant breast epithelial cells, while the receptors for PDGF reside only on stromal cells[27]. Other human studies have also confirmed the tendency for certain growth factors to be localized in stromal tissue[28]. These findings suggest that PDGF increases breast epithelial proliferation by stimulating stromal cells that display their cognate receptors to produce another growth factor (IGF) which, in turn, is mitogenic for breast epithelial cells[25].

In addition, stromal tissue also acts as a reservoir of growth factors. The extracellular matrix binds many growth factors, as well as proteases and protease inhibitors[29,30]. These proteases and protease inhibitors facilitate the activation of latent growth factors and the release of bound factors[29]. Thus, the extracellular matrix sequesters a variety of growth factors that can be readily activated, and plays a major role in the growth of the mammary epithelium. The stroma not only regulates the growth and differentiation of normal mammary epithelium; it also has a regulatory role in the infiltrative growth of cancer. For epithelial malignancies (carcinomas), the mesenchyme or stroma is the regulatory environment for neoplastic development and progression. In hormone-dependent cancers, this regulatory environment is modified by past and present exposure to hormones, which controls the stromal reservoir of growth factors. Breast cancers are unusual in that they are typically very desmoplastic, the stroma accounting for the majority of the tumour volume. This stromal microenvironment influences the behaviour of the neoplastic epithelium[31]. For example, DeCosse *et al.*[32], using a murine mammary tumour, demonstrated different rates of tumour growth with different stromas. Furthermore, the stromal cells surrounding cancer cells are phenotypically different from those within non-cancerous breast tissue[25,33], and the former have raised levels of growth factors and proteases[28,30]. The changing composition of the surrounding stroma with age probably accounts for part of the large difference in local recurrence rates between the very young and the elderly.

Effect of age on growth factor activity

As mentioned previously, during ageing there is a profound change in the relative proportion of stromal, epithelial and adipose tissue components, which in turn affects the growth factor content of the breast. Many reports demonstrate that levels of growth factors and growth factor receptors decrease with age[34–38]. There is an age-dependent decrease in growth hormone and serum IGF-1 levels, beginning after 30 years of age[34,35]. Decrease in the levels of these factors induces the atrophy of muscle, bone and skin and contributes to the frailty of the elderly.

In the young breast, normal growth during the lobular stage of development is associated with the highest levels of IGF-1[39]. Involution, beginning at the preclimacteric phase, is related to a decline in growth factors[40]. In the postmenopausal group (aged above 55 years), where involution is nearly complete, levels of oestrogen and growth factors are quite low[27].

Oestrogen and growth factors as tumour promoters

Clinical data have linked a woman's lifetime exposure to oestrogen and progesterone with the development of breast cancer. This observation is based on the increased cancer risk associated with early menarche, late menopause, late first full-term pregnancy and nulliparity. Oöphorectomy markedly decreases the proliferation of mammary tissue and rapidly involutes the breast. There is a direct relationship between the degree of protection against breast cancer development and age at oöphorectomy[41,42]. Bilateral oöphorectomy performed before 35 years of age is associated with a 64 per cent reduction in the risk of breast cancer, compared with a reduction of only 32 per cent when performed in women aged 35–39 years[42]. Women who have never had hormonally functioning ovaries demonstrate a near total absence of breast cancer; they have an incidence of breast cancer similar to that observed in men[43]. These hormonal influences on breast cancer rates result from effects on epithelial cell replication; such cell division is essential to the genesis of human cancer[44].

Breast cancer risk tends to correlate directly with the age at which involution occurs. However, if the process of involution becomes interrupted after its commencement, but before its completion, by a late first pregnancy, the mammary epithelial cells are again stimulated into proliferation. The resulting delay in involution might lead to the persistence of epithelial and stromal elements older breasts which could, conceivably, increase the risk breast cancer[45].

Oral contraceptives have been implicated in promoti breast cancer; their influence on breast epithelium complex. Since they are administered during a time wh the ovaries are functional and since they inhil gonadotropin secretion, ovarian steroidogenesis reduced. Furthermore, since the combined influence oestrogen and progesterone during the luteal phase of t natural menstrual cycle maximizes mitotic activity, there concern that oral contraceptives may further increa breast proliferation. One study[13] showed that the rise the proliferative index of mammary epithelial cells w related to the potency of the oestrogen but not t amount of progesterone used. However, clinical studi do not reveal any consistent association between brea cancer rates and different formulations of o contraceptive[46–48]. The minimal dose of sex stero necessary to provide acceptable contraception appears produce total breast proliferation rates very close to tho occurring during a natural cycle[10,13,49]. After correcting f age and phase of the menstrual cycle, Anderson *et al.* reported increased breast epithelial proliferation with o contraceptive use only in nulliparous women, whereas t parous breast was almost unaffected. Review population-based epidemiological studies shows modestly increased risk of breast cancer associated wi long-term use of oral contraceptives in younger, but n older, women[50,51]. This increased risk in younger wom may be balanced by a subsequent long-term reduction breast cancer risk in older women who have discontinu use for over 10 years[52]. However this paradoxical ris protection effect might not apply to all subgroups (ve young and/or nulliparous). Although many studies[53– found duration of oral contraceptive use before a fu term pregnancy was associated with a greater cancer ri than use thereafter, such results have been questioned[51, Statistically, pregnancy tends to be followed for sever years by an increased risk of breast cancer, until a lon term protective effect resulting from changes in t susceptibility of breast tissue (i.e. postlactation involution) predominates[3,57]. Thus, studies focusing very young patients with breast cancer associated with t contraceptive pill may find smaller risk differentials if t short-term effect of a full-term pregnancy is an increase breast cancer risk[58]. Longer follow-up of at least 10– years of young nulliparous women using the pill necessary to confirm this hypothesis, suggested by son preliminary results with long-term use of o contraceptives[53,56].

Perhaps the least appreciated hormone-related ri factor for breast cancer is the extent and pattern mammographic density within the breast. Mammograph density reflects the amount of epithelial and strom elements relative to the proportion of fat, which radiologically translucent. Parenchymal densities noted mammography are closely associated not only with a but also with hormone-related breast cancer ri factors[59–64]. Several controlled studies[59,60,65,66] support association between dense mammographic parenchym patterns and an increased risk of breast cancer. The studies provide strong, although indirect, evidence for t hypothesized role played by involutional parenchym changes in determining breast cancer risk. Individu with greater than 50–75 per cent of the breast occupi by mammographic density have 3–5 times the risk developing breast cancer as compared to those of the same age with the least amount of mammographic density[60,66]

Oza and Boyd[65] suggest that the percentage of mammographic density may reflect the potential growth factor activity of the breast stroma. This suggestion is consistent with the hypothesis that an excess of growth factors promotes breast cancer. Experiments in mice have demonstrated that overexpression of several growth factors and their receptors is a strong risk factor for mammary cancer[67]. Younger age is associated with a very dense mammographic pattern and would be expected to be associated with high growth factor activity. Postmenopausal women have less mammographic density which would be associated with diminished growth factor content[59,61,68]. For a given age and menopausal status, women with relatively greater mammographic density (and thus greater growth factor capacity) have the greater cancer risk. Oestrogen replacement therapy after menopause is associated with increased breast parenchymal density in 24 per cent of patients[69], while therapy with tamoxifen, oöphorectomy, or administration of gonadotropin-releasing hormone agonist (GnRHA)[70] in premenopausal women results in a routine decrease in mammographic density. All of these mammographic density changes that occur with hormonal changes appear to reflect changes in proliferation of the epithelial and stromal elements. The greater the involutional changes that the breast undergoes, the less the mitogenic response to stimulation by hormones[3]. Oestrogen is much less effective in stimulating the completely involuted atrophic breast, as that tissue is a poor source of oestrogen-induced growth factors[27]. The controversial association between oestrogen replacement therapy and breast cancer risk in postmenopausal women[71–73] might suggest that once involution has progressed sufficiently, the effects of exogenous oestrogens on cancer risk are minimal[45]. This is supported by the relative lack of mammographic density increase after initiation of oestrogen replacement therapy in postmenopausal woman[69]; it is most evident in women who have probably completed breast involution (i.e. multiparous women over 56 years of age)[74]. However, the type of hormone replacement may have a determinant role in cancer risk, as the addition of progestin to oestrogen appears to increase mammographic density more readily[69,75–77]. It cannot be determined from clinical studies using a relatively short follow-up whether breast cancer incidence is affected by such combined hormonal therapy. However, older epidemiological studies on the age of both surgical and natural menopause illustrate that the effects on breast cancer incidence are not appreciated for 10–20 years, and that such hormonal effects last throughout the remainder of the individual's lifetime[42,58,78]. In contrast, any effect that 5 years of combined hormone replacement therapy might have probably will not become evident until the latency period reaches 15 years. Any earlier effects on breast cancer rates are likely to reflect stimulation of pre-existing cancers, and not the proliferative effect that such hormones have on normal postmenopausal breast tissue which might contribute to new cancers.

Oestrogen and growth factors affect tumour progression

The concept of ovarian influence on breast cancer was first recognized by Cooper in 1836[79]. He noted that breast tumours often fluctuated in size during the menstrual cycle, demonstrating 'shrinkage' at the beginning of each cycle, as well as at the onset of menopause. These observations led logically to surgical castration for advanced premenopausal breast cancer, as first reported by Beatson in 1896[80]. This line of reasoning was quite remarkable since it was developed before the discovery of steroid sex hormones four decades later[81]. Subsequent clinical studies with hormone manipulation have noted a 30–35 per cent response rate in unselected patients with metastatic breast carcinoma, and up to an 81 per cent response rate in oestrogen receptor-positive/progesterone receptor-positive cancers[82,83]. As two-thirds of breast cancers contain varying amounts of oestrogen receptor[84], hormone manipulation either alone or in combination with chemotherapy is a mainstay of clinical practice. The importance of growth factors in breast cancer progression has been reviewed recently[85].

Tumour recurrence: role of cancer cell stimulation at the time of surgical resection

The microenvironment of growth factors in the breast maintains a low (basal) level of growth factor activity if it is unstimulated by sex steroid hormones. However, growth factor activity is increased temporarily during tissue repair following breast surgery and is further enhanced by sex steroid stimulation[86]. At surgical resection, the same growth factors expressed by cells that mediate inflammation and tissue repair (i.e. platelets, macrophages, lymphocytes, fibroblasts and endothelial cells) are also involved in cancer proliferation[22]. The growth factor/cytokine signals required for repair of damaged tissue can also be recognized by neoplastic cells. The chemoattractant, mitogenic and angiogenic effects of such growth factors might support any stray cancer cells left behind at operation[87].

At the time of breast cancer resection, the microenvironment of the partial mastectomy wound is enriched with growth factors, not only from the invading inflammatory cells but also from the sex hormone-regulated epithelial–stromal cells in the breast tissue adjacent to the surgical site. This enriched growth factor microenvironment can modulate implantation, local invasion, survival and growth of otherwise fragile tumour cells shed at surgery which would otherwise not survive[87]. The following considerations demonstrate how the hormonal environment and breast tissue composition (as reflected by the woman's age) at the time of tumour resection will affect cancer recurrence.

The hormonal environment at the time of breast cancer surgery affects survival

Recently, serious consideration has been given to the consequences of performing breast cancer surgery during different phases of the menstrual cycle. Clinical studies have determined that timing of breast surgery with respect to the menstrual cycle affects prognosis. The majority of studies find that the luteal phase is the optimal period for performing surgery[88], although McGuire and colleagues[89] questioned whether these findings might result from chance alone. By dividing the menstrual cycle arbitrarily into enough subgroups, there is a high probability of finding a statistically significant difference in one of the groups. A recent meta-analysis of 21 published studies demonstrated a statistically significant ($P = 0{\cdot}02$) effect on prognosis[90]: there was a 16 per cent reduction in the 5-year mortality rate for surgical treatment performed during the luteal phase. Three of the larger studies[91–93] allowed closer scrutiny of the data by displaying prognostic results for each day of the menstrual cycle. Their results are remarkably similar in terms of favourable and unfavourable days for performing cancer surgery (*Table 2*).

These studies indicate that the least favourable timing for breast cancer surgery is the second week of the menstrual cycle (the late follicular phase), when apoptosis is minimal. The increased growth factor activity that blocks apoptosis is attributed to the oestrogen that is rising and peaking unopposed during this period, and which can upregulate growth factor receptors (EGF receptors)[94] and stimulate stromal cells to secrete growth factors[92]. Furthermore, oestrogen protection from apoptosis may persist for 1–2 days after withdrawal of unopposed oestrogen[18], allowing for an unfavourable result on the 14th day of the cycle when the oestrogen level is beginning to fall. This effect of increased growth factor activity blocking the apoptotic pathway in the late follicular phase may allow any tumour cells shed at operation to gain a selective growth advantage. In contrast, optimal surgical results are obtained in the late luteal phase of the cycle and into the first 2 days of menstruation, during which there are decreasing or low levels of oestrogen. Maximal cellular apoptosis occurs during the late luteal phase when stromal growth factors are in an inactive state and unable to support the growth of stray cancer cells. Extension of the days of best prognosis into the first 2 days of the subsequent cycle[92] may result from a preponderance of parous women, who tend to have a few days' delay in their peak point of proliferative activity (and thus in their peak day of apoptosis) compared with nulliparous women[12]. In addition, women who have regular menstrual cycles lasting longer than the typical 28 days tend to have a longer follicular phase, but the luteal phase is relatively unaffected and lasts approximately 14 days after ovulation[14].

The importance of the hormonal environment at the time of surgery can also be appreciated by analysing breast cancers diagnosed in postmenopausal women concurrently taking oestrogen replacement therapy. An

Table 2 Prognosis related to days elapsed from the onset of menstruation (day 1) until cancer surgery

Reference	Year	Endpoint	No. of patients	Days of the cycle	
				Best prognosis	Worst prognosis
Senie *et al.*[93]	1991	Recurrence	283	20–30* (especially last 5 days)	7–14
Veronesi *et al.*[91]	1994	Recurrence	1175	20–33*	10–14
Badwe *et al.*[92]	1991	Death	249	18–2†	3–14 (especially 6–11)

*Menstrual cycles lasting longer than the typical 28-day cycle; †extension into the first 2 days of the subsequent cycle

Table 3 Relationship between age and local recurrence

Reference	Year	Operation	Follow-up	Age (years)	No. at risk	Local recurrence (%)
Donegan *et al.*[104]	1966	RM	5 years	<40	41	47
				40–59	249	22
				≥60	414	12·5
Kurtz[100]	1992	L + RT	11 years	<35	109	18·4
				35–50	702	12·7
				51–65	618	9·2
				>65	254	7·5
Haffty *et al.*[99]	1994	L + RT	6·4 years	<35	46	11
				35–50	152	7
				>50	350	4
Fowble *et al.*[101]	1994	L + RT	8 years	<35	64	19
				35–50	363	9
				>50	553	6·5
Veronesi *et al.*[106]	1993	Quad; no RT	39 months	<45	63	17·5
				45–55	104	8·7
				>55	106	3·8
Veronesi *et al.*[107]	1995	Quad + RT	8·5 years	≤35	168	13
				36–45	690	11
				46–55	723	4·4
				56–65	454	2·9
				>65	198	4
Harris and Recht[108]	1991	L + RT	8·5 years	<35	62	24
				35–50	335	14
				51–65	256	10
				>65	130	3

Local recurrence is defined as tumour arising in the remaining treated breast tissue or the chest wall. RM, radical mastectomy; L, lumpectomy; Quad, quadrantectomy; RT, radiotherapy improved prognosis has been found consistently in such individuals[95–97], although this association should be interpreted cautiously. The improved survival has been attributed partially to more careful breast screening, resulting in an earlier diagnosis, as well as reflecting tumours with more favourable prognostic factors[95–97]. Alternatively, the improved survival might be attributed to a precipitous downregulation of the hormonal milieu, since these women presumably had their replacement therapy withdrawn more than 1–2 days before operation. These results are consistent with the importance of a hormonal environment that minimizes growth factor activity and maximizes apoptosis at the time of surgery.

Patient age as a prognostic predictor of local recurrence

The age of the patient with breast cancer at the time of breast-sparing surgery is an independent prognostic factor for local recurrence[98–103]; this may even apply after mastectomy[104,105]. *Table 3* summarizes seven major series addressing this issue. Age less than 35–40 years is consistently associated with a higher local recurrence rate than age over 55–65 years[99–101,104,106–108]. The youngest age group has nearly double the average local recurrence rate of all age groups[109] and four to six times the rate of the oldest group alone[99,100,103,104,106–108].

The reasons for this continuously decreasing risk of local recurrence with age are elusive[110]. Several theories have been advanced to explain why younger age has such an adverse effect on local recurrence.

Proliferation rate. There is evidence that age is inversely related to the proliferation rate of both normal as well as cancerous breast tissue[111–113]. Olsson *et al.*[114] have suggested that, in young women, breast tumours proliferate at higher rates characteristic of normal breast tissue at that age. A more rapid proliferative rate in younger hosts could also explain their higher rate of early relapse and rapid evolution of disease[115,116]. Cancers in the elderly, on the other hand, have a lower proliferative rate similar to that of their non-neoplastic epithelial cells. Furthermore, even tumours that occasionally show high proliferative rates in older women tend to be more indolent, suggesting additional protective effects on local recurrence related to increased age[116].

Tumour histopathology. Younger patients tend to have prognostically worse histological types of breast carcinoma, including inflammatory carcinoma, than patients over 50 years of age[113]. Older women more commonly have tubular and colloid carcinoma, oestrogen receptor-positive/progesterone receptor-positive status and low S phase tumours than do younger patients[117]. On multivariate analysis using other histopathological variables, young age remains a statistically significant risk factor for local recurrence[109,115,118]. Fisher *et al.*[118] evaluated 32 histopathological factors in a regression analysis of predictive factors for in-breast recurrence after lumpectomy and radiation therapy; they concluded that age less than 35 years is statistically the most important prognostic variable.

Pathology of residual breast tissue. Patients with breast cancer under the age of 40 have a worse prognosis regardless of surgical treatment modality (lumpectomy, quadrantectomy or mastectomy), indicating that multifocal disease, as the cause of increased local recurrence in the young, plays only a minor role. Furthermore, most pathological studies on mastectomy specimens fail to show any relationship between age and multicentricity[119]. There are scattered reports, however, indicating a greater amount of residual microscopic carcinoma in completion mastectomy specimens from younger women. This might be predicted, as tumours with an extensive intraductal carcinoma component are commoner in younger individuals. One study[120] investigated the incidence of multicentricity at a distance from the index tumour after simulated breast-conserving surgery. A total of 183 cases of ductal carcinoma treated by mastectomy and examined pathologically using 0·5-cm whole breast sections were investigated. At distances over 2·5 cm from the index tumour, there was a direct correlation between age less than 40 years and residual microscopic cancer. Using 4·5-cm margins from the index tumour (margins which would approximate to a quadrantectomy), however, a converse correlation was evident (*Table 4*). As the breast-sparing trials that employ quadrantectomy[106,107] also demonstrate a higher local recurrence rate in younger patients, residual cancer foci in the immediate vicinity of the index tumour are unlikely to account for the age effect.

Young age as a resistance factor to radiation therapy. This is suggested by the multivariate analysis of the National Surgical Adjuvant Breast Project B-06 Trial, wherein young age was a significant risk factor for local recurrence in the group treated with lumpectomy and radiotherapy, but was no longer significant in the group of patients treated by lumpectomy without radiation therapy[118]. However, three other randomized trials evaluating breast-conserving surgery[106,121,122] found young age to be the most important risk factor, even in the non-irradiated group.

Young age as a resistance factor to adjuvant chemotherapy. Adjuvant chemotherapy exerts its greatest benefit in premenopausal patients. However, this benefit is not as evident in those below 35 years of age. In this age group a relative lack of treatment response may be explained partially by the reduced rate of chemotherapy-induced menopause[123]. However, this worse prognosis with young age is also evident in the node-negative groups that did not receive any adjuvant treatment[123].

Young age is associated with a richer endocrine hormonal environment. Kurtz[110] has suggested that the increased rate of local recurrence in young women is due to their higher oestrogen levels. The importance of modulating the hormonal environment in the young patient with breast cancer before operation was first recognized by

Table 4 Relationship between age and multicentricity using 2·5- and 4·5-cm surgical margins around the index cancer

	Multicentricity	
Age (years)	2·5-cm margin	4·5-cm margin
<40	9/23 (39)	2/23 (9)
40–59	41/124 (33)	15/124 (12)
≥60	9/36(25)	5/36 (14)

Values in parentheses are percentages. Of 183 cases, six were non-invasive ductal carcinomas and 177 invasive ductal carcinomas. Modified from Morimoto *et al.*[120]

Table 5 Age and site of in-breast recurrence and contralateral cancer

Age (years)	No. of patients	Development of breast tumours		
		Ipsilateral breast		
		Same quadrant as primary (surgical site)	Elsewhere (other quadrant)	Contralateral breast
Harris and Recht[108]*				
<35	62	13 (21)	2 (3)	7 (11)
35–50	335	33 (9·9)	12 (3·6)	25 (7·5)
51–65	256	24 (9·4)	3 (1·2)	12 (4·7)
≥65	130	3 (2·3)	1 (0·8)	8 (6·1)
Veronesi *et al.*[107]†				
<35	168	18 (10·7)	4 (2·4)	10 (6·0)
36–45	690	56 (8·1)	20 (2·9)	35 (5·1)
46–55	723	28 (3·9)	4 (0·6)	33 (4·6)
56–65	454	12 (2·6)	1 (0·2)	26 (5·7)
≥65	198	5 (2·5)	3 (1·5)	6 (3·0)

Values in parentheses are percentages. Patients were followed up for 8·5 years after *lumpectomy and radiotherapy or †quadrantectomy and radiotherapy

Schinzinger in 1889[124]. He noted that young patients had a very poor prognosis and recommended that oöphorectomy be performed in these women before, or along with, the mastectomy, in order to 'involute' the breast and to 'contain tumour cells'[124,125]. Horsley in 1944[126] furthered this concept, believing that the small number of residual cancer cells left after radical mastectomy could be stimulated by oestrogenic substances. He further hypothesized that oöphorectomy would have its greatest benefit during the perioperative period. The acute withdrawal of oestrogen would create an unfavourable 'soil' which should be deleterious to the survival and implantation of any cancer cells remaining after mastectomy. In the light of today's knowledge, this acute involution of the breast with preoperative or perioperative oöphorectomy results from decreased growth factor activity, which maximizes apoptosis.

A further explanation for local recurrence rates decreasing with age considers not only the endocrine environment but also the level of growth factor activity at the surgical site. The importance of this latter factor is emphasized by the results of two large clinical studies[107,108] (*Table 5*). Age less than 35 years strongly influences the development of recurrent cancer in the same quadrant as the surgical site, but plays only a minor role in the development of cancer either in other quadrants of the ipsilateral breast or in the contralateral breast. These data cannot be explained by the effects of oestrogen alone on any remaining cancer cell. Rather it is hypothesized that this predilection for in-breast recurrence at the surgical site is attributable to the growth factors that concentrate locally at the site of injury. These growth factors can stimulate any free floating residual cancer cells that have been shed at surgery or any focus of ductal carcinoma *in situ* that remains in the breast in close proximity to the surgical bed[87]. Therefore the tendency for recurrence at the original site is not merely due to multifocal disease around the index tumour. This predilection for the site of surgery occurs even after quadrantectomy, when all microscopic disease within the index quadrant has been removed.

The lower rate of local recurrence in the older patient with breast cancer is accounted for by the inverse correlation of growth factor activity with age. The very low incidence of local (in-breast) recurrence in the elderly suggests that breast involution protects against local recurrence by presenting a diminished growth factor milieu at the surgical site following partial mastectomy. This lower growth factor activity in the elderly after surgical wounding may result not only from decreased levels of growth factor secretion but also from reduced expression of growth factor receptors.

Irrespective of the patient's age and breast composition, manipulation of the endocrine hormonal environment can modulate growth factor activity[86]. Optimal surgical management, therefore, needs to be timed to minimize the effects of an oestrogen-rich environment, which augments the inventory and concentration of growth factors in the mammary stroma and epithelium, and which upregulates growth factor receptors. Operations should be timed for when oestrogen protection against apoptosis is at a minimum[17]. Malignant cells shed during cancer surgery under conditions of unopposed rising or peaking oestrogen may be better able to survive, proliferate and develop into local recurrences or micrometastases. In contrast, cells shed during periods of maximal apoptosis, i.e. when mammogenic growth factor activity has just been withdrawn, should be least able to survive.

Conclusions

Appreciation of the interplay between endocrine and paracrine hormones in normal as well as in neoplastic breast proliferation has allowed a re-evaluation of our thoughts on the host–cancer relationship. It has given impetus to study the need for hormonal manipulation in chemopreventive trials in high-risk individuals. Additionally, recognition of this hormonal interplay invites consideration of preoperative or perioperative therapies to offset the endocrine/growth factor stimulatory effects which vary with age, menstrual cycle status and breast composition. Breast surgeons have the capability of performing surgery in a setting of diminished growth factor capacity. To achieve optimal results in terms of lowered local recurrence and increased overall survival, the influence of growth factors on cancer cells must be minimized; this can be accomplished to some degree by operating when maximal apoptosis is present. Antioestrogens, somatostatin analogues and GnRHA should be evaluated in the perioperative setting in terms of manipulation of the endocrine and paracrine hormonal environment. Data generated from prospective trials will allow breast surgeons to determine the optimal hormonal strategy for maximizing the benefits of their operative effort.

Acknowledgements

The authors thank Ms D. Kleinmuntz, Ms L. Feinberg, Ms J. McLemore, Ms S. Swanson, Ms G. Murat and Ms M. Oviedo for assistance in searching out and retrieving articles. They also thank Ms M. Jelachich for translating German references.

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British Journal of Surgery 1996, 83, 1047–1055

Review

Anal transitional zone and columnar cuff in restorative proctocolectomy

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The popularity of double stapling the ileal pouch–anal anastomosis probably owes more to the technical ease it brings than to histological considerations or functional results. It is preservation of a 'columnar cuff' of mucosa, rather than the restricted site of the anal transitional zone, that should be the focus of research with respect to long-term risk of malignancy and inflammatory complications. If cancer is present in colon that has been removed for ulcerative colitis, there is a 25 per cent incidence of dysplasia in the columnar cuff in the short term. In other circumstances, those who are spared from carcinoma by colectomy are likely to have a similar risk of developing dysplastic change in the columnar cuff with longer follow-up. Double stapling the pouch–anal anastomosis and preserving the anal canal mucosa improves function, but long-term surveillance of the columnar cuff is then required, including biopsies.

Restorative proctocolectomy is the successful culmination of considerable surgical endeavour over recent decades to improve the quality of life for patients who require proctocolectomy for ulcerative colitis or familial adenomatous polyposis (FAP). Having established it as the procedure of choice for most of these patients, the goal now is to minimize the morbidity of surgery and to achieve good long-term function with perfect continence.

One of the original precepts of restorative proctocolectomy was that all the potentially diseased mucosa, including the anal transitional zone (ATZ), should be removed to eliminate colonic disease. Many surgeons believe they have been doing this by the technique of mucosectomy above the dentate line. Close examination, however, reveals that reliably achieving complete excision by this method is unrealistic. Histological examination of excised pouches has confirmed the presence of islands of rectal mucosa between the pouch and the 5–8-cm rectal muscle cuff of earlier procedures[1,2]. These islands did not show any evidence of proliferation or active disease and generally caused no problem in the long term, although it has been suggested that they may contribute to postoperative pelvic sepsis[3]. The only four cases of cancer reported within a pouch have, however, involved patients who had mucosectomy and it seemed that the cancers arose from areas of residual mucosa[4–7]. Such concern, and the observation that the long muscle cuff serves no useful purpose, have resulted nowadays in the retention of only a very short rectal cuff.

In the mid-1980s improved surgical staplers led to the technique of double stapling and this was soon applied to the ileal pouch–anal anastomosis. This, in combination with a stapled J pouch, led to the introduction of the totally stapled restorative proctocolectomy[8,9]. The comparative technical ease of this procedure makes it favoured by many. It is quick to perform, there is little potential for contamination and some have suggested a particularly low leak rate from the pouch–anal anastomosis. The technique involves anastomosing to the top of the anal canal, the epithelial lining of which is retained. The retained mucosa consists of the ATZ and a cuff of columnar epithelium between the ATZ and the stapled pouch–anal anastomosis (*Fig. 1*). Much current debate centres on the probable functional advantage of retaining the anal canal mucosa *versus* the disadvantage of potential malignancy in the columnar epithelium of both the ATZ and the columnar cuff. In recent years there has emerged a population of patients with a history of severe ulcerative colitis who are now retaining some diseased mucosa for life; this brings a need for lifelong follow-up of the retained mucosa.

The anal transitional zone in health and disease

The ATZ is frequently mentioned with regard to restorative proctocolectomy, but the more subtle aspects

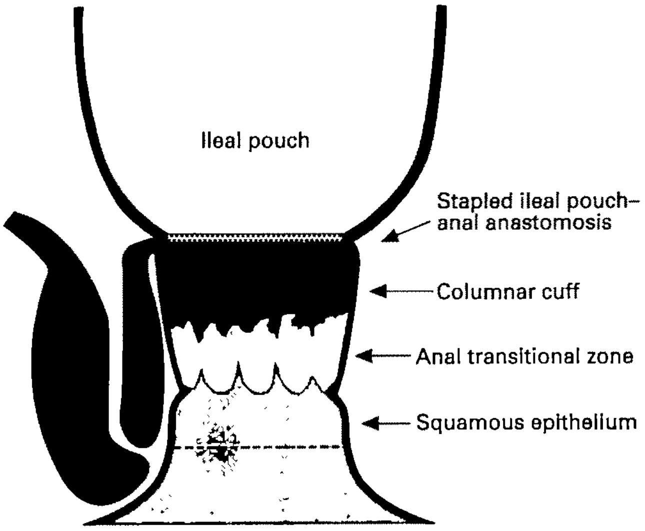

Fig. 1 Epithelial components of the anal canal after restorative proctocolectomy. The columnar cuff extends to the pouch–anal anastomosis which, in some cases, will be slightly above the anal canal. The dentate line, although variable, is usually situated at the lower end of the anal transitional zone

Paper accepted 19 March 1996

of its anatomy are infrequently appreciated. In the embryo, the anal membrane is situated caudad to the anal crypts and columns, and not at the level of the anal valves as is commonly believed. The anorectum is, therefore, of hindgut origin and, when the anal membrane ruptures at 7 weeks' gestation, the anal canal is endodermally lined by stratified cuboidal epithelium, as is the remainder of the gut at this stage[10]. Following rupture, ectodermal squamous epithelium creeps in a cephalad direction into the anal canal to reach the anal sinuses, leaving a variable amount of transitional epithelium above its upper extent before the commencement of columnar epithelium[11]. Over the years a confusing plethora of terminology has been used to describe the epithelial lining of the anal canal. Much of this has arisen because the extent of transitional epithelium varies considerably at different points in the anal canal and also between individuals. Early authors examined only a few cases each, with limited numbers of sections, and produced an array of differing descriptions.

Walls[12] brought some clarity to the situation with a description of 20 cases. Fenger[13] described a useful technique to define the ATZ in a whole specimen by staining with alcian blue (*Fig. 2*). The mucin-rich columnar epithelium stains dark blue and the mucin-poor transitional epithelium stains light blue; squamous epithelium does not stain. The ATZ may then be observed macroscopically and in a way that more clearly demonstrates its implications for the surgeon, as opposed to reading a description of a series of histological sections. After outlining this technique, Fenger[14] described the macroscopic appearance of whole-mount preparations of 113 anuses and checked this against the histology. The anal canals were noted to be about 3 cm in length. The dentate line ranged from 5 to 19 mm above the lower end of the anal canal, as defined by the lower border of the internal sphincter, with a mean height of 11·4 mm. Generally, the ATZ was located above the dentate line, but in eight canals it extended 3–6 mm below the dentate line. In 100 cases the ATZ started at the dentate line and extended upwards, and in four canals the lowest point of the ATZ started 1–7 mm above the dentate line. One canal had no evidence of an ATZ. Over the series, the ATZ ranged from 6 mm below the dentate line to 20 mm above. The mean span was 8·9 (range 0–20) mm. This work has established the current definition of the ATZ as 'the zone interposed between uninterrupted crypt bearing colorectal type mucosa above and uninterrupted squamous epithelium below'. It is important to reflect on this definition as many surgeons inappropriately refer to all the remaining anal canal mucosa after a stapled pouch–anal anastomosis as the ATZ when, in reality, a significant amount is columnar cuff, which is above the upper limits of the ATZ. Another practical point is that, if a biopsy from the anal canal contains columnar epithelium, it may be from the ATZ or columnar cuff and, similarly, if a biopsy reveals squamous epithelium, it may be from the ATZ or below it.

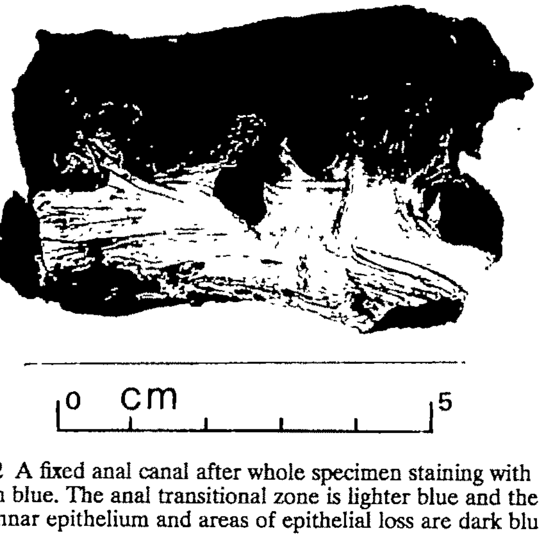

Fig. 2 A fixed anal canal after whole specimen staining with alcian blue. The anal transitional zone is lighter blue and the columnar epithelium and areas of epithelial loss are dark blue

Ambrose *et al.*[15] used alcian blue staining to identify the ATZ in 50 abdominoperineal specimens with ulcerative colitis and compared these with 50 control samples removed for cancer. Biopsies were taken from the ATZ to examine for inflammatory change. The varied extent and epithelial make-up of the ATZ was confirmed. Histological examination showed that in ulcerative colitis the columnar epithelium within the ATZ had inflammatory changes similar to those present in the rectum. The transitional epithelium, however, was not involved and had the same inflammatory score as controls. These authors advised caution in retaining the ATZ as this invariably meant retaining diseased columnar mucosa within its boundaries.

Histological considerations

There are two main histological considerations. First, what mucosa is either removed or left behind? Second, what evidence of disease is there in this mucosa? Most studies are based on surgical specimens from a mucosectomy or from stapler doughnuts and some have reported short-term follow-up with biopsies of the 'ATZ'. The following discussion reflects the situation at or shortly after operation but does not necessarily reflect the disease activity in the long term.

Mucosectomy specimens

The most extensive reported series of mucosectomy specimens[16] describes the risk of dysplastic or malignant disease in the anal canal mucosa in ulcerative colitis (*Table 1*), and of adenomas and dysplasia in FAP (*Table 2*). If there was a cancer in the proctocolectomy specimen of ulcerative colitis, there was a 25 per cent incidence of dysplasia in the anal mucosa. Mucosectomy was recommended as obligatory for patients with FAP and advisable in the presence of colorectal cancer. If ulcerative colitis had been present for more than 10 years, the incidence of dysplasia in the mucosectomy was 7·9 per cent; for less than 10 years the incidence was zero. These values may overstate the risk of retaining dysplastic anal mucosa at the time of operation for a double-stapled pouch–anal anastomosis, as the first 52 of 132 patients had the rectum divided 6–8 cm from the anal verge, which would permit much more mucosal stripping for analysis than with double stapling. However, it may be field change that is important and more limited sampling of a smaller mucosectomy may underestimate the longer-term risk.

Gilchrist *et al.*[19] (*Table 1*) recently published a study of 94 cases of mucosectomy during restorative proctocolectomy for ulcerative colitis. The distal 4–5 cm of the specimen, including the ATZ, was examined separately from the rectum and the presence of transitional or

Table 1 Presence of dysplasia or cancer in the anal mucosa of patients having restorative proctocolectomy for ulcerative colitis

Reference	*n*	Specimen*	Follow-up (months)	UC present	No. with dysplasia	No. with cancer	Risk of columnar cuff dysplasia in relation to histology of proctocolectomy specimen (%)		
							Cancer	Dysplasia	UC only
King *et al.*[17]	16	Mucosectomy	—	14	4 (25)	1	—	—	—
Tsunoda *et al.*[16]	118	Mucosectomy	—	—	3 (3)	0	25	0	1
Curran *et al.*[18]	12	Mucosectomy	—	12	0 (0)	0	—	—	—
Gilchrist *et al.*[19]	94	Mucosectomy	—	60 (acute)	15 (16)	0	—	—	—
Curran *et al.*[18]	12	Doughnut	—	12	0 (0)	0	—	—	—
Schmitt *et al.*[20]	45	Doughnut	—	19	0 (0)	0	—	—	—
Deen *et al.*[21]	38	Doughnut	—	38	0 (0)	0	—	—	—
Emblem *et al.*[22]†	19	Biopsy	36–60	7	0 (0)	0	—	—	—
Schmitt *et al.*[20]	38	Biopsy	8·4	10	0 (0)	0	—	—	—
Ziv *et al.*[23]	254	Biopsy	27	—	2 (1)	0	25	10	0
Slors *et al.*[24]	6	Biopsy	18	—	0 (0)	0	—	—	—

Values in parentheses are percentages. *From mucosectomy or distal stapler doughnut at operation or biopsy at subsequent follow-up if the anal transitional zone and columnar cuff are preserved; †straight ileoanal anastomosis. UC, ulcerative colitis

squamous epithelium was confirmed in all specimens. No information was given regarding the presence of dysplasia or carcinoma in the remainder of the colon and rectum, but the authors provided a good argument for mucosectomy and a strong case for long-term monitoring if the ATZ and a columnar cuff are retained.

Two further reports of mucosectomy specimens are summarized in *Table 1*; these include one carcinoma that was not revealed until histological examination of the mucosectomy[17,18]. Of significance is the fact that dysplasia was noted in the rectum of this patient. There are no reports of carcinoma developing in a columnar cuff after its deliberate retention to enable a double-stapled pouch–anal anastomosis to the top of the anal canal, although anal canal cancer has been reported after a straight ileoanal anastomosis in a patient with FAP[25].

Distal doughnuts from stapled anastomoses

The reports of doughnut histology from restorative proctocolectomy are summarized in *Tables 1* and *2*. In both the larger series[20,21] the frequent presence of transitional and squamous epithelium showed that significant portions of anal canal mucosa were being removed. This removes more diseased tissue and retains the convenience of stapling but is likely to compromise function. Deen *et al.*[21] were aiming to staple half their cases at the dentate line and to compare the results with anastomosis at the top of the anal canal. They demonstrated in lower pouch–anal anastomoses that they were not actually able to staple to the dentate line, as evidenced by doughnut histology and the mean anastomotic height of 2·9 cm. Furthermore, these doughnuts showed inclusion not only of rectal wall, but also of external sphincter that was being crushed in the stapler. Functional results were inferior in the group with the low pouch–anal anastomosis[26].

It is routine practice to submit both mucosectomy specimens and stapler doughnuts for histology. The few published results suggest that the only changes noted are the expected inflammatory changes of ulcerative colitis and diversion colitis (if the rectum was defunctioned). The evidence from examining doughnuts and mucosectomy specimens at the time of pouch formation does not support an argument for routine mucosectomy. Exceptions to this occur for FAP, ulcerative colitis complicated by rectal cancer and, probably, colonic cancer. The critical question is: what long-term changes will develop in the columnar cuff? The final answer may not be revealed for another 30 years, but useful information is presently available from long-term follow-up of patients who have undergone ileorectal anastomosis.

Table 2 Presence of polyps or dysplasia in the anal mucosa of patients having restorative proctocolectomy for familial adenomatous polyposis

Reference	*n*	Specimen*	Follow-up (months)	Adenoma present	Dysplasia
Tsunoda *et al.*[16]	14	Mucosectomy	—	12	12
Deen *et al.*[21]	4	Doughnut	—	4	0
Emblem *et al.*[22]†	13	Biopsy	44	10	0
Slors *et al.*[24]	1	Biopsy	28	1	0

*From mucosectomy or distal stapler doughnut at operation or biopsy at subsequent follow-up if the anal transitional zone and columnar cuff are preserved; †straight ileoanal anastomosis

Ileorectal anastomosis in ulcerative colitis

The studies with longer follow-up are derived from series before biopsy surveillance was widely practised. There is a risk of developing rectal cancer of 15–20 per cent at 25–30 years after ileorectal anastomosis[27,28]. With a shorter follow-up period of 10–20 years, the risk is substantially less at 0–6 per cent[28–33]. The chance of developing cancer is much less if there is neither dysplasia nor cancer in the resected colon[27]; this is consistent with the information reported on dysplasia in mucosectomy specimens by Tsunoda *et al.*[16]. Filipe *et al.*[34] described six patients who developed carcinoma and two with severe dysplasia following ileorectal anastomosis. All eight were monitored with regular mucosal biopsies but four of the cancers arose without any warning from such surveillance. This raised concerns about the reliability of surveillance, particularly for patients at high risk[34].

The area of a fixed anal canal containing glandular epithelium is approximately 1·5 × 5·0 cm and the rectum is

15·0 × 8·0 cm. This means that about 6 per cent of the mucosa at risk is retained with a pouch–anal anastomosis to the top of the anal canal. This may translate into a risk of cancer of about 1 per cent at 30 years, doubling if a further 1–2 cm of mucosa is left above the anal canal, as inevitably happens in some cases. This assumes that the columnar cuff behaves in a similar manner to the rectum after ileorectal anastomosis. It has been postulated that the decreased inflammatory activity seen in the rectum after such an anastomosis leads to a decrease in proliferative activity and, therefore, to a reduction in risk of cancer[35]. A similar change might take place in the columnar cuff. Treatment of the rectum after ileorectal anastomosis has been reported to result in regression of dysplasia associated with epithelial recovery[36], suggesting a possible role for treating the columnar cuff. However, it may be argued that the features that regressed may not have been true dysplasia but regenerative changes in the base of the crypts. The prediction of risk of malignant change in the columnar cuff from studies of ileorectal anastomosis for ulcerative colitis may be affected by the possibility that some patients had this type of operation because of relative distal sparing. Such patients might represent a different phenotypic group from that of the majority of patients having restorative proctocolectomy in the modern era.

In general terms, carcinoma complicating ulcerative colitis has a similar distribution to sporadic cancer but is multiple in 20–30 per cent of cases, usually involving different segments[37–39]. If colonic cancer is present in a resected specimen, after thorough sampling, dysplasia may be expected in the rectum (including the anal canal) in 65 per cent of cases; this incidence falls to 55 per cent with colonic dysplasia but no cancer[39].

Genetic predisposition for cancer in ulcerative colitis

A large cohort study[37] suggested that patients with extensive colitis have a genetic predisposition to colorectal cancer and that long-standing inflammation is not of primary importance in the initiation or promotion of neoplastic change. Cotton-topped tamarin colitis, which provides the closest animal model of ulcerative colitis in humans, lends support to this concept (B. F. Warren, personal communication). The genetics of inflammatory bowel disease are complex[40], but it is possible that a phenotypic expression of cancer may represent a genotype that would benefit from mucosectomy. Preoperative identification is a possibility for the future.

Ileorectal anastomosis in familial adenomatous polyposis

Estimation of risk can be made for ileorectal anastomosis in FAP just as for ulcerative colitis. At the age of 60 years, the risk of developing rectal cancer after ileorectal anastomosis for FAP is 14–29 per cent, and probably increases in the decades that follow[41,42]. This translates into a risk of about 2 per cent of developing carcinoma in the restricted site of the columnar cuff. The risk of rectal cancer after ileorectal anastomosis has been shown to increase with an increasing number of polyps in the rectum, and is likely to be greater in those with mutations with a more aggressive phenotype[43]. In FAP it seems that there is usually adenomatous disease in anal canal epithelium (*Table 2*). Although the risk of carcinoma may not be excessive, polyps below the pouch–anal anastomosis are likely to cause functional problems, either through their presence or the need for repeated polypectomy in patients who already, by the nature of their surgery, have less than optimal continence. These considerations, however, may not apply to those with attenuated forms of FAP[44,45] whose phenotypic presentation is later, with rectal sparing and limited colonic polyposis. Mucosectomy seems advisable for many patients with FAP. If mucosectomy is not carried out initially and there is a problem with polyposis in the anal canal after pouch surgery, this can be treated by mucosectomy and pouch advancement[46].

Biopsies of the anal transitional zone and columnar cuff

Malignant potential. It is important to continue to monitor a retained columnar cuff in the anal canal. There is limited information on histological follow-up of the cuff after restorative proctocolectomy; this is summarized in *Tables 1* and 2. Generally, biopsies are described as taken from the 'ATZ' with an anoscope in outpatients, but the epithelial components of biopsies are often not reported. The difficulty of reliably identifying the ATZ on anoscopy and the pain induced by biopsying it suggest the authors may have been biopsying columnar cuff rather than ATZ. Ziv *et al.*[23] reported that initially eight patients had low-grade dysplasia but, on repeat biopsies, this persisted in only two; this raises the question as to whether this was a diagnostic error or a sampling problem[47]. There was neoplastic change in the colectomy specimens of the two with persistent dysplasia in the anal canal, and the risks of developing columnar cuff dysplasia if there is cancer (25 per cent risk) or dysplasia (10 per cent risk) in the proctocolectomy specimen are similar to those described in the mucosectomy study of Tsunoda *et al.*[16]. Emblem *et al.*[22] reported on straight ileoanal anastomosis, aiming to preserve 1–2 cm of anal mucosa in 32 patients. Of interest, apart from the recurrence of adenoma in patients with FAP, is that at 2 years the anal mucosa was 3·9 cm long despite the initial notion that at operation only 1–2 cm was left. Are there influences, for example increased tension on the upper anal canal, that enable a pouch–anal anastomosis to move cephalad?

Both low- and high-grade dysplasia are predictive of future carcinoma, and dysplastic changes are much more common in the rectosigmoid region than in the remainder of the colon[47]. Although the majority of patients having restorative proctocolectomy are now left with a columnar cuff, little is known about the behaviour of this tissue after operation. The limited information available and outlined here suggests that those likely to be at greatest risk from malignant change in retained columnar epithelium are patients with FAP or with ulcerative colitis and associated dysplasia or cancer in the proctocolectomy specimen. The presence of aneuploidy in ulcerative colitis in non-dysplastic mucosa is an early and sensitive marker for the development of low-grade dysplasia[48–50]; *p53* point mutations correlate closely with the development of aneuploidy and may also be present in non-dysplastic mucosa[51]. Now that many patients with ulcerative colitis retain anal canal mucosa for the duration of their lives, these markers may be useful in providing early warning of trouble in the columnar cuff. The cuff should be biopsied regularly to establish its 'natural' history and ensure safety in the longer term, as is the practice for ileal pouch mucosa.

Inflammatory changes.. The inflammatory changes of ulcerative colitis are usually present in the columnar epithelium of the anal canal at the time of proctectomy[15,18,20] but, notably, the transitional epithelium is spared from such changes[15,51]. There are reports confirming the presence of inflammation in the anal canal after restorative proctocolectomy[20,52], but only Lavery *et al.*[53] have clearly presented a series of follow-up biopsies in which the epithelial type is confirmed and the incidences of histological and symptomatic inflammation are recorded. They reviewed 217 patients after restorative proctocolectomy for ulcerative colitis in whom the anal canal mucosa was preserved. These patients had anal canal biopsies at a mean follow-up of 30 months. Endoscopic anal examination revealed mild or moderate inflammation in 33·2 per cent and severe inflammation in 2·3 per cent. Colonic-type cells were noted in 72·4 per cent of biopsies, and histopathology demonstrated mild to moderate inflammation in 76·5 per cent and severe inflammation in 5·5 per cent. Anal canal inflammation, determined by endoscopy and confirmed by histopathology, was present in 22·1 per cent, and this was associated with pouch inflammation in 13·8 per cent. Symptomatic inflammation occurred in 14·7 per cent in the form of urgency, pain and bleeding. Symptoms generally settled with local or systemic (if the pouch was inflamed) treatment. The type of mucosa present in the biopsy was not correlated with presence or severity of inflammation and no comment was made on the contribution a previous diversion proctitis may have had on subsequent inflammation in the anal canal. Medical treatment does not always result in the resolution of symptoms[54] and there are two reports of severe inflammation in the anal canal requiring respectively a mucosectomy[54] and pouch advancement[55]. However, problems from inflammation in the columnar cuff and ATZ are usually minor and easily treated; they do not provide an argument for routine mucosectomy.

Function

The anal canal mucosa has a rich sensory innervation[56]; it is highly sensitive to pain, touch and temperature. The ability to detect very small changes in temperature in the anal canal is thought to enable the appreciation of wetness. This sensory capability, combined with the sampling of rectal contents allowed by the rectoanal inhibitory reflex, enables discrimination of flatus from stool[57]. Loss of temperature sensitivity, which is most acute in the mid-anal canal, has been demonstrated in incontinent individuals[58], and anal mucosectomy carried out during restorative proctocolectomy also results in a loss of sensation[59].

Apart from the desirability of maintaining the anal canal mucosa for better function, most surgeons retain the ATZ and columnar cuff because it allows the technical advantage of double stapling the pouch–anal anastomosis. In itself this is, arguably, inadequate justification in the light of the risk (albeit small) of retaining a remnant of colitic columnar epithelium. Against this can be set the increasing evidence for an actual as well as theoretical functional gain from less disturbance to the anal canal. However, it should be noted that amputating the rectum at the pelvic floor may still have profound yet poorly documented effects on anal function, due to the division of the myenteric plexus which certainly affects descending innervation. There are no reports of mucosectomy a hand-sewn pouch–anal anastomosis to the dentate li having a physiological or functional advantage ov stapled pouch–anal anastomosis to the top of the an canal. On the contrary, almost all reports show physiological gain from the latter technique whi frequently translates into a functional advantage. In area where the number of patients is often small a where satisfactory controlled studies are not realisti these observations may be the best evidence to suppo the avoidance of mucosectomy. One larger serie reported that leaving the anal canal undisturb significantly decreased the small risk of major faec leakage; two of 111 *versus* 15 of 110 had major nocturn leakage. Most of the argument, however, centres damage to the internal sphincter as a cause of loss of t finer control of continence. This loss results in increas minor leakage, particularly at night, and po discrimination and control of flatus.

Randomized trials

Seow-Choen *et al.*[61] published one of the two prospecti randomized trials comparing hand-suturing and staplin They showed a significantly smaller drop in resting an pressure (RAP) with stapling but no functional differenc with 15–20 per cent of patients in both groups havi mucous leakage. However, with only 28 patients in t final analysis, a pelvic sepsis rate of over 20 per ce (likely to decrease pouch compliance and affe function[62]) and four of the stapled anastomoses requiri reinforcement with hand sutures, it is unlikely that th study could unearth a moderate advantage for eith technique. There was no correlation between time of an dilatation (recorded for both procedures) and the drop RAP, because the senior surgeon who carried out t operations undoubtedly used minimal anal retractio One other similar study by Luukkonen and Jarvinen containing a total of 40 patients, found no difference function or physiology between the two techniques, a both groups had a 30 per cent drop in RAP. McIntyre *al.*[64] concluded that there was no functional advantage stapling after comparing 27 consecutive stapled cases wi 27 matched hand-sewn cases. However, the night-ti incontinence rate of 41 per cent in this stapled group w higher than that in most other reports. These studies ha not answered the question of whether one techniq provides a functional advantage.

Function and internal sphincter physiology

Tuckson *et al.*[65] published a useful paper describing 1 patients, which compared no manipulation *vers* manipulation of the anal canal. There was, respectively, minor leakage rate of 14 *versus* 43 per cent at night, a 6 *versus* 16 per cent by day, and a major leakage rate of *versus* 12 per cent at night, and 2 *versus* 2 per cent by da These differences were accompanied by a significan greater drop in the RAP in the manipulation grou These authors also compared hand-sewn endoanal pouc anal anastomosis with and without mucosectomy, a showed similar results in favour of no mucosectomy. hand-sewn pouch–anal anastomosis with mucosectom compared with a double-stapled pouch–anal anastomos results in varying combinations of poorer continenc lower RAP, loss of the rectoanal inhibitory reflex (RAI and decreased anal sensation[59,66–77]. Some authors ha reported that double stapling causes similar internal sphincter impairment to mucosectomy[78,79], and this is particularly so if attempts are made to staple down into the anal canal to enable anastomosis to the dentate line[26,80]. Despite a poorer outcome in terms of physiology[80], Braun and co-workers[81] have recently described good functional results with stapling into the anal canal. The balance of evidence, however, favours stapled anastomosis to the top of the anal canal. A large randomized trial is now unrealistic and impractical.

Can normal anal physiology be retained?

Long-term studies following stapled pouch–anal anastomosis outline very good physiological and functional results. Sagar *et al.*[82] studied 20 patients before and 3, 7 and 12 months after stapled pouch–anal anastomosis. While there was a decrease in RAP and loss of the RAIR at 3 months, these features had returned virtually to normal at 12 months. At a mean of 6 months' follow-up, in a later series from the same institution, Lewis *et al.*[83] showed that RAP had almost returned to normal, that the RAIR (or pouch–anal inhibitory reflex after surgery) was present in all and that anal sensation was preserved in all. Clinically, two of 30 patients had some nocturnal leakage, 25 could discriminate flatus from stool and 13 were confident enough to pass flatus without a visit to the toilet. The two aspects of function that are most important to patients are leakage and urgency. These recent results are certainly an improvement over series reporting minor incontinence or nocturnal leakage rates of around 40 per cent with mucosectomy and hand-sewn pouch–anal anastomosis[64,84–88]. It seems likely that poorer function and a lowered RAP result from a combination of loss of anal sensitivity, anal manipulation and the trauma of mucosectomy.

Anorectal innervation and the rectoanal inhibitory reflex

The detail of the neuroanatomy and neurophysiology of the RAIR is not completely understood. Evidence suggests the reflex is mediated intramurally by the anorectal myenteric plexus, with nitric oxide as the neurotransmitter[89]. It is also subject to modulation by the autonomic nervous system[90]. With adequate follow-up after anterior resection, the RAIR returns in 85–100 per cent of cases[91–95]; it has also been reported to return after a straight ileoanal anastomosis with mucosectomy[96]. Following hand-sewn pouch–anal anastomosis with mucosectomy, the RAIR has returned in 0–33 per cent[60,69,71,97] and after a double-stapled pouch–anal anastomosis to the top of the anal canal in 5–100 per cent[71,80,83,84]. Recovery of the RAIR over time with an end-to-end anastomosis[83] may be associated with nerve regeneration across the anastomosis that is not possible with mucosectomy and sleeving the pouch into a short muscular cuff.

In the dog, the return of the RAIR after low colorectal anastomosis has been correlated with regeneration of autonomic nerves at the anastomotic site[98]. However, other experimental evidence suggests regeneration is much less likely if the anastomosis is between different regions of intestine[99] (small and large intestine) and also if the anastomosis is not truly end to end[100] (which includes J and W pouches). Farouk *et al.*[79] observed return of the RAIR in only one of 23 stapled cases at 1 month and again at 18 months, and noted that in this case 1 cm of rectum was inadvertently retained. It is possible that a short segment of rectum (1–2 cm) must be retained to preserve the RAIR following restorative proctocolectomy. If it is deemed that maintaining the RAIR is important for the finer control of continence and it is already acceptable to retain 1·5 cm of columnar mucosa in the anal canal, adding a further 1 cm of rectal mucosa above this, on current information, may not cause a problem, but to advocate this would be controversial. However, reports of the presence of the RAIR after restorative proctocolectomy could mean that some are already falling short of the target of anastomosing to the top of the anal canal. More careful and objective reports on anastomotic height 1–2 years after restorative proctocolectomy would be useful to clarify this issue, especially in the light of the already described experience of Emblem *et al.*[22].

Internal sphincter morphology

Silvis *et al.*[101] recently reported on internal sphincter morphology after pouch construction. They recorded endoanal ultrasonographic findings in 23 patients following restorative proctocolectomy. Nineteen patients had a hand-sewn pouch–anal anastomosis with mucosectomy and four had a double-stapled pouch–anal anastomosis. There was significant thinning of the internal sphincter in all patients compared with normal controls. In most this was uniform, but in six patients with hand-sewn pouch–anal anastomosis there was tapering of the internal sphincter, with gaps in two. These six cases suggest evidence of trauma and it is possible that uniform thinning might be explained by either dilatation or denervation. There was no correlation between ultrasonographic findings and function or physiology.

Morbidity

On a practical note, the double-stapled anastomotic technique must lessen the risk and extent of pelvic contamination as at no time are there open ends of bowel in the pelvis. It would be difficult to prove that this potentially reduced contamination results in a decreased rate of pelvic sepsis, but some surgeons have reported this to be their experience[60,102]. There is also evidence that double stapling is associated with a decreased pouch–anal anastomotic leak rate[103,104].

Conclusions

A clear understanding of the histology of the anus is important in restorative proctocolectomy. The ATZ and a columnar cuff are usually retained if the pouch–anal anastomosis is double stapled. The columnar cuff contains most of the remaining diseased epithelium that is at risk of inflammatory problems and malignant change, and the authors propose the wider use of the term 'columnar cuff' in future publications on the retained anal canal mucosa. Those who have ulcerative colitis associated with high-grade dysplasia or colorectal carcinoma should have a mucosectomy, as should those who have FAP with a degree of rectal polyposis or a suspected high-risk genotype. In other cases, the risk of retaining the anal mucosa seems small, but regular long-term follow-up with biopsies of the columnar cuff is necessary, as it is probable that a small number will develop premalignant changes. A functional advantage accrues from a double-stapled pouch–anal anastomosis to the top of the anal canal, expressed as a substantially reduced risk of minor anal leakage.

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British Journal of Surgery 1996, 83, 1056–1058

SURGERY TODAY
The Japanese Journal of Surgery

Digest

Dr Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the January, February and March 1996 issues of his journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Oesophageal carcinoma

The effects of hypergastrinaemia on chemically induced carcinogenesis in the oesophagus were studied[1]. Operations were performed on 5-week-old male Donryu rats as follows: (1) truncal vagotomy plus pyloroplasty (group V), (2) segmental gastrectomy plus pyloroplasty (group G), (3) antrectomy (group A), and (4) no operation as a control (group C). From the age of 6 weeks, the animals were given 0·003 per cent *N*-methyl-*N*-amylnitrosamine (MAN) solution as drinking water for 8 weeks. After 20 weeks of MAN administration, the animals were bled and killed. The average serum gastrin levels in groups V and G were significantly higher than those in groups C or A. There were significant differences between groups C and V in the incidence of carcinoma, and between groups V and A in the incidence of carcinoma including severe dysplasia. The incidence of histologically identified lesions per animal was determined, and significant differences were observed between group C and both groups V and G in the incidence of carcinoma including severe dysplasia. Gastrin receptors were detected in the oesophageal lesions produced by oral administration of MAN to rats. The results suggest that endogenous hypergastrinaemia has a positive influence on chemically induced carcinogenesis in the rat oesophagus.

Another study was conducted to examine the long-term outcome of 500 patients who underwent surgery for cancer of the thoracic oesophagus during the past 20 years[2]. Favourable results were obtained with postoperative adjuvant radiation and chemotherapy and there were no surgical deaths in the last 5 years. The mortality rate decreased from 17 per cent before 1980 to 5 per cent between 1981 and 1993, this being most probably attributable to the decreased incidence of suture-line leakage. With respect to changes in surgical technique, during the initial years, the authors performed intrathoracic anastomosis, after which sternal manubrium resection with anterior mediastinal oesophagogastrostomy was carried out. Subsequently, a technique was developed for performing oesophagogastrostomy via the posterior mediastinum. The posterior mediastinum was selected as the most physiological route, based on measurement of tissue oxygen tension. Using blood flow determination obtained by laser Doppler velocimetry, it was concluded that the effectiveness of thicker gastric tubes was superior to that of thin tubes. Oesophagogastrostomy was performed in a shallow field in the cervical region, with the anastomosis ultimately positioned in the superior mediastinum and covered with mediastinal pleura.

Gastric carcinoma

Kubota *et al.*[3] investigated the modulating effect of recombinant human interferon (IFN) alpha-2a on the antitumour activity of UFT, a mixed compound of tegafur and uracil at a molar ratio of 1:4, against SC-1-NU, a human gastric cancer xenograft serially transplanted in nude mice[3]. IFN was administered subcutaneously at a dose of 60 000 units per mouse daily for 14 days, and UFT was given at a dose of 15 mg/kg as tegafur daily, except on Sundays, for 3 weeks. The agents were administered either alone or simultaneously. Synergistic antitumour activity on SC-1-NU was produced by the combination of IFN and UFT without any increment of side-effects; the combination therapy also increased intratumoral thymidylate synthetase inhibition and the amount of 5-fluorouracil in the intratumoral RNA. Thus, IFN alpha-2a seems to modulate the antitumour activity of UFT against SC-1-NU by inhibition of DNA synthesis and RNA distortion; this combination could therefore be useful for clinical application.

Papillary clear carcinoma (PCC), a variant of gastric papillary adenocarcinoma, demonstrates the histological features of cancer cells with clear cytoplasm and no nuclear polarity, resembling the primitive gut epithelium of the fetus[4]. To clarify the clinical and prognostic characteristics of PCC, the authors examined operative specimens from 73 patients with gastric papillary adenocarcinoma. Light microscopic examination of haematoxylin and eosin stained sections of specimens from 15 patients revealed the features of PCC. Patients with PCC demonstrated a higher incidence of type 3 gross appearance, tumour invasion into the muscularis propria or beyond, involvement of distal lymph nodes, liver metastasis, raised serum α-fetoprotein concentration and palliative resection. In two subsets of patients who underwent curative resection of tumours invading the muscularis propria or beyond, those with PCC were found to have a significantly lower survival rate than those with other types of papillary adenocarcinoma ($P<0{\cdot}05$). PCC histology was a significant prognostic determinant according to multivariate analysis with the Cox proportional hazards model. The authors conclude that this subclassification of papillary adenocarcinoma, based on the cellular findings, is a useful prognostic indicator, and that intensive adjuvant therapy may be indicated for patients with the features of PCC, even if they have undergone a curative resection.

Recent advances in the quantitative assessment of bone mineral content have resulted in an increasing awareness of metabolic bone disease as a late complication following gastrectomy. In a study by Nihei *et al.*[5], 98 patients who had undergone gastrectomy were examined by quantitative computed tomography. Bone mineral density index (BMDI), defined as 100 × (measured bone mineral density/bone mineral density of age- and sex-matched controls), was used to evaluate the effect of gastrectomy on bone disorders. Mean(s.d.) BMDI following gastrectomy was 80(27), with no significant difference between men and women, or between total and distal gastrectomy. Moreover, no significant difference was observed between mean(s.d.) BMDI within 6 months of gastrectomy, 93(37), and that at 6 months to 1 year after gastrectomy, 80(31); however, a significant and sharp decrease to 70(36) was evident after 1–2 years. The regression coefficient of the BMDI measured within 2 years after operation was lower than that measured after 2 years. These findings suggest that the influence of gastrectomy on bone metabolism is induced within 2 years, after which the bone mineral content decreases in accordance with physiological nature. Thus, the authors conclude that the treatment for bone disease resulting from gastrectomy would only be effective if initiated within a short period after surgery.

Colon cancer

Bile acid composition was assessed in 50 patients with colorectal cancer and compared with that in a control group of 50 age- and sex-matched subjects[6]. The overall bile acid values were similar in both groups, while the relative concentrations of primary and secondary bile acids were different, a significant increase in the patients with colorectal cancer being observed. This finding seems to confirm the existence of a link between colorectal cancer and cholelithiasis. Both conditions share common risk factors, such as alterations in cholesterol metabolism and bile acid composition.

Another group[7] reported the results of a retrospective study conducted on patients who developed recurrence following surgery for colorectal cancer. The authors present a practical plan to improve survival rates. Of 974 patients who underwent surgery for colorectal cancer during the 20 years between 1974 and 1993, 152 developed recurrence: local recurrence in 70 (7·2 per cent), liver metastasis in 47 (4·8 per cent) and pulmonary metastasis in 35 (3·6 per cent). The number of patients who underwent reoperation or curative resection was 54 of 70 and 13 of 54 respectively of those with local recurrence, 16 of 47 and six of 16 of those with liver metastasis, and six of 35 and six of six of those with pulmonary metastasis. The 3- and 5-year survival rates were 13 and 9 per cent respectively after reoperation for local recurrence, 14 per cent and nil after reoperation for liver metastasis, and 53 and 53 per cent after reoperation for pulmonary metastasis. Although evaluation was difficult owing to the small number of patients with lung metastasis, resection of a pulmonary lesion resulted in a good outcome. Furthermore, a significant difference in 3- and 5-year survival rates was observed between patients who underwent reoperation and those who had conservative treatment, for whom the 3- and 5-year survival rates were nil following local recurrence, 5 per cent and nil following liver metastasis, and nil following lung metastasis. These findings indicate that aggressive surgery for recurrence may result in a better outcome.

Liver disease

A study was conducted to clarify whether endotoxin-induced liver injury could be improved by modulating the function of hepatic macrophages using OK432, an immunostimulant derived from *Streptococcus*[8]. OK432 increased the capacity of hepatic macrophages to produce superoxide and tumour necrosis factor (TNF), and enhanced the messenger RNA (mRNA) expression of interleukins 1α and 1β, and TNF-α in liver non-parenchymal cells (NPC). However, intravenous pre-administration of OK432 reduced the endotoxin-enhanced mRNA expression of TNF-α in liver NPC, decreased the serum level of glutamic oxaloacetic transaminase and lactic dehydrogenase (LDH), and improved the survival rate of endotoxin-injected rats. Histological examination revealed a significant reduction in cell vacuolization and focal necrosis in the livers of endotoxin-injected rats pretreated with OK432. These results indicate tl hepatic macrophages play a crucial role in endotox induced liver injury, and that TNF-α is one of the fact most likely to be implicated in the development endotoxin-induced liver injury. Thus, it is suggested tl the administration of OK432 provides liver protection modulating the responsiveness of hepatic macrophages endotoxin.

Kitagawa *et al.*[9] examined how the effects of dopami and dobutamine on hepatic blood flow are influenced obstructive jaundice in a conscious canine model. Befc biliary obstruction, portal venous blood flow (PV increased in response to the infusion of either dopami or dobutamine: dopamine infused at 8 μg per kg per m produced a mean(s.d.) increase of 19(0) per cent in PV while dobutamine infused at 16 μg per kg per m produced an increase of 30(2) per cent. Although hepa arterial blood flow (HAF) decreased dose-dependently response to the infusion of dopamine, no significa change was observed in HAF in response to any dose dobutamine. Obstructive jaundice attenuated completely abolished the stimulatory effect of dopami on PVF, whereas it did not significantly alter the effect dobutamine on hepatic blood flow. In dogs wi obstructive jaundice, dopamine at 16 μg per kg per m produced a mean(s.d.) decrease in PVF of 17(3) per ce These findings suggest that dobutamine is more effecti than dopamine for increasing hepatic blood flow patients with obstructive jaundice.

The effect of OKY-046, a thromboxane A_2 syntheta inhibitor, on hepatic dysfunction produced by liver c ischaemia was studied in an experimental model of ra with obstructive jaundice[10]. The experiments we performed 7 days after the rats underwent bile du ligation. Warm total ischaemia of the liver was induced Pringle's method over a 20-min period and the anima were divided into two groups with or without OKY-04 The reperfusion time was 30 min in each group. OKY-0 was administered via the femoral vein at a rate of 100 per kg per min from 15 min before the blockade to t end of the experiment. The level of adenosi 5′-triphosphate in the liver tissue of the OKY-046 grou was raised slightly, but not significantly, compared wi that of the control group. The ratio of thomboxane B_2 6-ketoprostaglandin $F_{1\alpha}$ in the liver tissue was lower in t OKY-046 group than in the control group; significa differences were found between the two groups in t water content of the liver and the mitochondrial score examined by transmission electron microscopy. Thus, was observed that an improvement in the balance thromboxane A_2 and prostaglandin I_2 associated wi OKY-046 administration protected the cellular structu of the mitochondria in rat liver.

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British Journal of Surgery 1996, 83, 1059–1061

Pulmonary function after laparoscopic cholecystectomy in the elderly

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The results of laparoscopic cholecystectomy in a group of 52 patients older than 69 years (group 1) were compared with the results of the same operation in a group of 338 younger patients (group 2). In group 1, 23 per cent of patients had acute cholecystitis and 13 per cent were operated on after an episode of acute pancreatitis. In group 2, 8 per cent of patients had acute cholecystitis and 4 per cent were operated on after acute pancreatitis. Pulmonary function was assessed prospectively before operation, 24 h after surgery and on the seventh day after operation, in 20 patients in group 1 and 30 in group 2. In group 1 there was one death (2 per cent); the morbidity rate was 14 per cent and conversion to laparotomy was required in 15 per cent. In group 2 there were no deaths, the morbidity rate was 11 per cent and the conversion rate 4 per cent. No significant differences were found between the two groups in mortality and morbidity rates. Preoperative values of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV$_1$) were significantly lower in group 1 than in group 2 ($P < 0\cdot05$); the values of FVC, FEV$_1$ and forced expiratory flow at 50 per cent 24 h after surgery were less depressed in group 1 ($P < 0\cdot01$) and also recovered more quickly in these patients 7 days after operation. Laparoscopic cholecystectomy gives excellent results in geriatric patients and can be recommended as the treatment of choice for symptomatic cholelithiasis in the elderly.

The continuing ageing of the Portuguese population has led to a significant rise in the number of patients submitted to operations such as cholecystectomy. The introduction of the laparoscopic approach, with its recognized benefits of less discomfort, shortened hospital stay and rapid return to normal activity, represents a new challenge and it is necessary to determine whether these benefits are also experienced by elderly patients, who are generally considered to have diminished cardiopulmonary reserve.

The increase in intra-abdominal pressure during pneumoperitoneum causes a decrease in lung compliance and a rise in peak inspiratory pressure. Atelectasis, reduced functional residual capacity, ventilation–perfusion mismatch and pulmonary shunting contribute to a decrease in arterial oxygenation[1]. Moreover, high insufflation pressures tend to compress the major abdominal veins (particularly the inferior vena cava), which compromises venous return and leads to a drop in preload and cardiac output in some patients[2]. When hypercapnia is allowed to develop, it may stimulate the sympathetic nervous system and thus increase blood pressure, heart rate and the risk of dysrhythmia. Although these effects are usually well tolerated in healthy people, they can be more serious in patients with impaired cardiac function, restrictive lung disease or intravascular volume depletion[3].

The aim of this study was to present the results of laparoscopic cholecystectomy in patients older than 69 years and to compare results with those obtained in the treatment of cholelithiasis in younger patients. The study also reports a prospective assessment of pulmonary function after laparoscopic cholecystectomy in both age groups.

Patients and methods

Between January 1992 and December 1994, 390 consecutive patients underwent laparoscopic cholecystectomy. Fifty-two (13 per cent) were 70 or more years old (group 1) and 338 were younger (group 2).

In group 1 the 52 patients (36 women) were of mean age 74 (range 70–90) years; 39 patients were classified as American Society of Anesthesiologists (ASA) grade I, ten as ASA II and three as ASA III. Mean(s.d.) weight and height were 68(15) kg and 1·56(0·09) m. Forty-one patients were found to have several stones in the gallbladder, nine had a single stone and two gallbladder adenoma. Twelve patients (23 per cent) were operated on for acute cholecystitis and seven (13 per cent) for acute pancreatitis of biliary origin. Three patients had had a previous episode of jaundice and 11 previous abdominal surgery. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) was performed in five patients and demonstrated stones in three. Pulmonary function was assessed prospectively in 20 consecutive patients before operation, 24 h after surgery and on the seventh day after operation. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$) and forced expiratory flow at 50 per cent (FEF$_{50}$) were measured. No patient was excluded from the study.

In group 2 the 338 patients (244 women) were of mean(s.d.) age 49·5(11) years; 278 patients were classified as ASA grade I, 51 as ASA II and nine as ASA III. Mean(s.d.) weight and height were 69(12) kg and 1·59(0·40) m. Some 249 patients were found to have several stones in the gallbladder, 70 had a single stone and 19 had gallbladder adenoma. Twenty-six patients (8 per cent) were operated on for acute cholecystitis and 13 (4 per cent) for acute biliary pancreatitis. Seven patients had a previous history of jaundice and 106 had undergone previous abdominal surgery. ERCP was performed on two patients and intravenous cholangiography on two more; nevertheless none of these tests showed stones in the common bile duct (CBD). Pulmonary function testing as described above was performed prospectively in 30 consecutive patients before operation, 24 h after surgery and on day 7. Again no patient was excluded from the study.

An operative cholangiogram was obtained in all cases of acute cholecystitis and acute pancreatitis, and in other patients at risk of common duct stones.

Statistical analysis

For statistical evaluation Student's *t* test and contingency table analysis were used in the program StatView 512+, version 1·01 (Abacus Concepts; Brainpower, Calabasas, California, USA), run on a personal computer. $P < 0\cdot05$ was considered significant.

Paper accepted 19 November 1995

Results

One patient in group 1 died (mortality rate 2 per cent). The patient, in whom conversion to laparotomy was required to repair a CBD injury, died from mesenteric infarction following a large haematoma of the transverse mesocolon. This patient suffered from von Willebrand's disease. Complications in group 1 consisted of loss of gallstones in the abdominal cavity ($n=3$), subcutaneous emphysema ($n=2$), bladder infection (in one patient with a Foley catheter waiting for urological surgery) and pneumonia ($n=1$) (total seven of 51 or 14 per cent). Conversion to laparotomy was required in eight patients (15 per cent) and was due to distorted anatomy ($n=7$) and CBD injury ($n=1$). A drain was left in three patients. The mean(s.d.) operating time was 76(29) min and median hospital stay after surgery was 3 days. Mean(s.d.) values of FVC, FEV_1 and FEF_{50} before operation were 2·3(0·78) litres, 2·0(0·7) litres and 3·2(1·4) l/s respectively. The changes from preoperative values are shown in *Table 1*.

There were no deaths in group 2. Complications were loss of gallstones in the abdominal cavity ($n=18$), subcutaneous emphysema ($n=6$), wound infection ($n=4$), bile leakage requiring laparotomy ($n=2$), perforation of the diaphragm ($n=2$), bleeding from a trocar site ($n=2$), intra-abdominal abscess (infected haematoma) ($n=1$), stenosis of the main bile duct (further laparotomy for repair) ($n=1$) and hepatic laceration ($n=1$) (total 37 of 338 or 11 per cent). In 13 patients a drain was left for 24 h and 14 procedures (4 per cent) required conversion to laparotomy, due to distorted anatomy ($n=12$), haemorrhage (posterior branch of the cystic artery) ($n=1$), and malfunction of the optical system ($n=1$). The mean(s.d.) operating time was 73(36) min and median hospital stay after surgery was 2·5 days. The mean(s.d.) values of FVC, FEV_1 and FEF_{50} before operation were 3·5(0·9) litres, 2·8(0·8) litres and 3·7(1·3) l/s respectively. The changes from preoperative values are shown in *Table 1*.

No significant differences were found between the two groups in sex distribution, weight, height, ASA grade, haemoglobin level, haematocrit, total plasma bilirubin, plasma alanine aminotransferase, mortality, morbidity, operating time and hospital stay. Apart from age significant differences were found in the mean(s.d.) levels of alkaline phosphatase (109(82) units/l in group 1 *versus* 73(43) units/l in group 2); the incidence of acute cholecystitis ($P=0{\cdot}0001$) and of acute pancreatitis ($P=0{\cdot}003$) were significantly greater in group 1 and there was a significantly higher rate of conversion to laparotomy in group 1. The preoperative values of FVC ($P=0{\cdot}001$) and FEV_1 ($P=0{\cdot}003$) were significantly lower in group 1 than in group 2. Both groups experienced a reduction of FVC, FEV_1 and FEF_{50} after operation but in group 2 the fall in values was greater than in group 1 (*Table 1*).

Table 1 Postoperative pulmonary function

	Group 1	Group 2	P
FVC			
Day 1	90(12)	72(19)	<0·01
Day 7	102(9)	97(8)	n.s.
FEV_1			
Day 1	88(10)	72(19)	<0·01
Day 7	100(4·3)	96(9)	n.s.
FEF_{50}			
Day 1	87(19)	64(20)	<0·01
Day 7	102(12)	91(18)	n.s.

Values are mean(s.d.) percentages of preoperative results. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF_{50}, forced expiratory flow at 50 per cent; n.s., not significant (Student's t test)

Discussion

Between 1980 and 1989 the proportion of the Portuguese population older than 65 years increased from 11·4 to 13·1 per cent[4]. As the incidence of gallstones increases with age, cholecystectomy has become a common operation in older people with consequent increased risks.

One of the goals of surgical treatment of the elderly is to give the best possible quality of life and to reduce surgical stress to a minimum. This may be achieved with the laparoscopic approach, which avoids laparotomy and reduces surgical trauma.

Laparoscopic cholecystectomy has now become the 'gold standard' for treatment of symptomatic gallstone disease. This approach was attempted in all of the present patients, irrespective of age, with symptomatic gallstone disease. The incidence of single or multiple stones was similar in both groups. However, acute cholecystitis, acute pancreatitis and common duct stones, common complications of biliary lithiasis, were more frequent in the elderly as reported in other studies[5–11]. The mean preoperative level of alkaline phosphatase was significantly higher in the older patients ($P<0{\cdot}05$). This is probably related to the higher incidence of acute cholecystitis, acute pancreatitis and common duct stones in this age group. Operative cholangiography was performed in all patients with acute cholecystitis and acute pancreatitis. The authors use this technique in a selective manner, as do many others[5,12–16].

Mortality rates for laparoscopic cholecystectomy vary from 0·04 to 0·9 per cent[10,17] and for open cholecystectomy from 0 to 3 per cent[6,18–20]. The present series of 390 consecutive patients includes one death (0·3 per cent). This is less than the reported mortality rate after open cholecystectomy in elderly patients of 3–12·7 per cent[7,21–26].

There was no significant difference between the two groups in complications. These results may be considered favourable when compared with the reported complication rates of 18–34·6 per cent after elective open cholecystectomy in elderly patients[7,22–26].

Patients in group 1 required a significantly higher number of conversions to laparotomy than those in group 2 (15 *versus* 4 per cent); this was also found in another report[5]. It reflects the chronicity of the disease resulting in a shrunken, fibrotic gallbladder and also reflects a higher incidence of acute cholecystitis and pancreatitis in this age group. Conversion to laparotomy was needed for distorted anatomy, except in one case.

The results of prospective pulmonary function testing showed that older patients have a reduced pulmonary reserve. Nevertheless, patients in group 1 experienced a smaller reduction in FVC, FEV_1 and FEF_{50} both 24 h and 7 days after surgery. These findings may indicate that, from this standpoint, laparoscopic cholecystectomy is the operation of choice for older people.

No significant differences were found between the two groups in operating time and mean hospital stay after surgery.

In conclusion, laparoscopic cholecystectomy gives good results in elderly patients and allows a comfortable postoperative course and rapid return to normal life. None of the variables analysed suggests any reason to preclude this approach and the authors believe there may be definite benefits of this treatment of symptomatic gallstones in older people.

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British Journal of Surgery 1996, 83, 1062–1064

Cholangiocarcinoma in patients with opisthorchiasis

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Cholangiocarcinoma is very common in areas endemic for the liver fluke *Opisthorchis viverrini*. Survival after surgical treatment of cholangiocarcinoma associated with opisthorchiasis was studied prospectively in 30 patients, all of whom resided in an endemic area. The median age was 52 (range 32–69) years and twenty-five patients were men. Seven patients had their tumours removed, four with concomitant liver resection. Twenty-two patients underwent palliative biliary bypass procedures to a segmental duct. Laparotomy with biopsy of metastatic lesions was undertaken in one patient with multiple lymph node metastases and peritoneal seedlings. No patient received postoperative chemotherapy or radiation treatment. Patients were followed for 2 years or until death. The 1-year survival rate after tumour resection was 86 per cent and the 2-year survival rate 43 per cent. After palliative procedures the 1-year survival rate was 26 per cent; no patient reached 2 years and the median survival time was 8 months. Survival after surgical treatment of cholangiocarcinoma in patients with opisthorchiasis is broadly similar to that reported for cholangiocarcinoma without liver fluke infestation.

Cholangiocarcinoma is common in Thailand particularly among people in the north-eastern region of the country, which is an area endemic for the liver fluke *Opisthorchis viverrini*[1,2]. The parasite is equally prevalent in Laos and parts of western Malaysia, where it infests the bile ducts of millions of people[3,4]. Approximately one-third of the rural north-east Thai population (or roughly 7 million people) harbour this fluke[5]. The crude annual incidence of cholangiocarcinoma in this population is 54 per 100 000 with an age-standardized incidence of 87 per 100 000, compared with 2 per 100 000 in Western countries[6].

Strong evidence of a close relationship between opisthorchis infestation and human cholangiocarcinoma derives from both case–control studies and epidemiological surveys[6–8]. In hamsters the combination of dimethylnitrosamine and 100 metacercariae (the infective form and dose of *Opisthorchis viverrini*) can induce cholangiocarcinoma in the liver[9,10]. Nitrosamine production may also be increased by an endogenous process following liver fluke infestation[11].

Operative treatment is the best available therapy for cholangiocarcinoma. Not only can it cure the patient at an early stage of the disease, but it can also provide effective palliation for those with irresectable tumours. However, survival after surgical treatment of cholangiocarcinoma in association with opisthorchiasis has never been adequately studied. The aims of this prospective study were therefore to elucidate the characteristics of this condition and to evaluate the long-term results of surgical treatment.

Patients and methods

Forty-eight patients with cholangiocarcinoma were treated between April 1992 and November 1994. Thirty-four of the 48 tumours were considered to be related to *Opisthorchis viverrini*. Of these thirty-four patients, four were lost to follow-up; the remaining thirty formed the basis of this study. Their median age was 52 (range 32–69) years and twenty-five were men. Criteria for a diagnosis of opisthorchiasis were: (1) a history of previous positive stool examination for opisthorchis or its eggs; (2) identification of opisthorchis or its eggs in the stool or bile; (3) demonstration of a typical bead-like cholangiogram (for patients undergoing a bypass procedure); and (4) histological evidence of the parasite in the resection specimen. All patients lived in an area endemic for *Opisthorchis viverrini*, had a long history of eating raw fish and had at least two of these criteria.

Patients were evaluated before operation for liver function, serum carcinoembryonic antigen (CEA) level, stool examination for the fluke or its eggs, and by abdominal ultrasonography and/or computed tomography. Visceral angiography was carried out in patients with possibly resectable tumours, and intraoperative ultrasonography was used as a supplement to operative exploration to determine the resectability of the lesion[12]. Suspected metastatic lymph nodes or peritoneal nodules were biopsied for histological examination without an attempt to biopsy the primary lesion. Patients with an irresectable tumour underwent palliative biliary segmental duct–enteric bypass over a 12–14-Fr stent. Bile taken from the stent during the first few days after operation was examined for the parasite.

No patient received postoperative chemotherapy or radiation treatment. Patients were scheduled to attend the clinic at 3-month intervals for up to 2 years after operation or until death. Those who were unable to visit the clinic were contacted regularly by post. Differences in 1-year and 2-year survival rates between patients undergoing either tumour resection or bypass were analysed by the χ^2 test.

Results

Preoperative data

Jaundice was the commonest presentation, occurring in 26 of the 30 patients. The median duration of jaundice was 4 (range 1–16) weeks, and the median serum total bilirubin level was 333 (range 40–638) μmol/l; normal is <17 μmol/l. The four anicteric patients presented with fever and chills associated with raised serum alkaline phosphatase and/or γ-glutamyl transferase activity. Abdominal and/or back pain was present in 18 patients; the median duration of pain was 4·5 (range 1–20) weeks. Median serum CEA level was 9·6 (range 1·8–925·4) ng/ml; normal is 0–3·4 ng/ml. Stool examination for *Opisthorchis viverrini* or its eggs was positive in four patients.

Perioperative data (Table 1)

All 30 patients had tumour in the area of the confluence of the hepatic ducts. Seven patients underwent tumour resection, four with concomitant hepatectomy, giving a

Paper accepted 14 March 1996

Table 1 Perioperative details of 30 patients with cholangiocarcinoma associated with *Opisthorchis viverrini* infestation

Type of operation	No.	Pathological findings
Resectional procedure		
Tumour resection with concomitant hepatectomy	4	Free surgical margin with no evidence of metastatic disease at operation
Local tumour resection	3	Two patients had free surgical margins with no evidence of metastatic disease One patient had metastatic cystic node and microscopic tumour at resection margin
Palliative procedure		
Segmental duct–enteric bypass	22	Multiple metastatic lymph nodes in 19 patients (one with pulmonary nodules suspicion of metastasis) Peritoneal seedlings in three patients
Laparotomy alone	1	Multiple metastatic lymph nodes and peritoneal seedlings

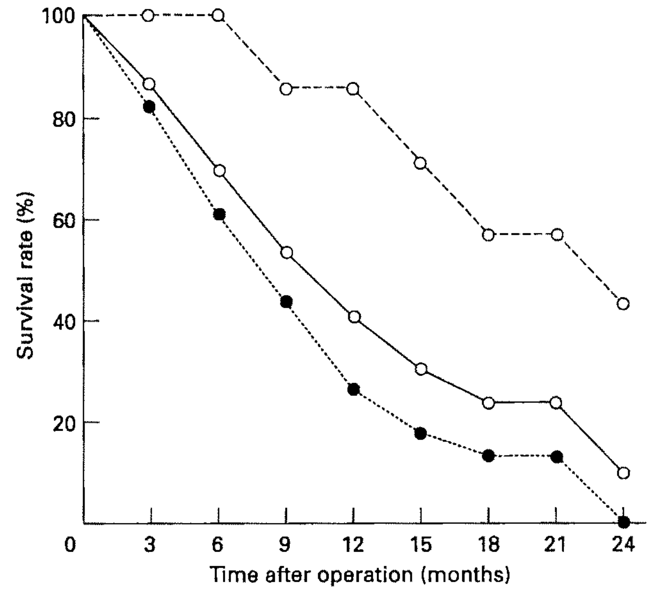

Fig. 1 Survival curves after surgical treatment of cholangiocarcinoma in patients with opisthorchiasis. ——O——, Overall ($n = 30$); ---O---, tumour resection ($n = 7$); ·····●·····, biliary bypass ($n = 22$). Survival after resection was significantly better than after bypass at 1 year ($P < 0{\cdot}005$) and 2 years ($P < 0{\cdot}001$) (χ^2 test)

resectability rate of 23 per cent. The four patients who underwent hepatectomy were anicteric before operation. One of the three patients undergoing local tumour resection had subsequent histological evidence of metastasis to the cystic lymph node plus microscopic tumour at the resection margin. Twenty-two patients underwent palliative segmental duct–enteric bypass (using the segment III duct in 18 patients and another segmental duct in four) owing to obvious metastasis in the cystic and/or retropancreatic lymph nodes (19 patients) or peritoneal seedlings (three). One patient had multiple lymph node metastases with peritoneal seedlings, and only biopsy of the metastatic lesion was performed. Thus 21 patients in this series (70 per cent) had metastatic lymph nodes and four had multiple peritoneal seedlings. These metastatic lesions were confirmed histologically.

There was no operative or hospital death. The 22 patients who underwent biliary bypass procedures had tube cholangiography performed 1 week after operation. Four of these patients had *Opisthorchis viverrini* or its eggs in the bile, all but one of whom had negative preoperative stool examination.

Survival (Fig. 1)

For those undergoing resectional procedures the actual 1-year survival rate was 86 per cent and the 2-year survival rate 43 per cent. Two of the three patients who survived beyond 2 years died, at 26 and 34 months. The other patient underwent re-exploration 22 months after the first operation because of jaundice, and was found to have recurrent tumour with multiple lymph node metastases. She is still alive 6 months after the second operation for biliary bypass, 28 months after tumour resection. The patient who underwent incomplete local excision died 7 months after operation.

After palliative biliary bypass procedures, all patients had at least one episode of fever with chills suggestive of cholangitis, but none required further admission until the final stages of the disease. The median survival in this group was 8 (range 1·5–22) months and the 1-year survival rate was 26 per cent. All patients died within 2 years. There was therefore a significant difference in 1-year survival rate ($\chi^2 = 48{\cdot}1$, 1 d.f., $P < 0{\cdot}005$) and 2-year survival rate ($\chi^2 = 9{\cdot}3$, 1 d.f., $P < 0{\cdot}001$) between patients with resection and bypass. The patient who underwent laparotomy alone died at 3·5 months.

Discussion

A considerable body of experimental and epidemiological data suggests that liver flukes, particularly *Clonorchis sinensis* and *Opisthorchis viverrini*, play an important role in the development of bile duct cancer[7,8,13–15]. Of the four criteria used to identify patients with opisthorchiasis in the present series, the cholangiographic appearances are based on the finding that the liver fluke produces an acute inflammatory reaction around the intrahepatic ducts and portal connective tissue leading to subsequent periductal and portal scarring[9,16]. In hamsters exposed to opisthorchis and nitrosamine, eradication of the parasite with the drug praziquantel did not significantly reduce the incidence of bile duct cancer[17]. Therefore any cholangiocarcinoma in a patient with a previous history of opisthorchiasis, whether or not they were treated, should be classified as opisthorchis-related cancer.

The resectability rate of hilar cholangiocarcinoma in this series (23 per cent) is lower than that of some recent reports[18,19] because most patients had multiple metastatic lymph nodes and/or peritoneal seedlings. The incidence of lymph node metastasis at the time of operation (70 per cent) is much higher than that reported in patients with hilar cholangiocarcinoma unrelated to the liver fluke (approximately 20 per cent)[19,20], likewise the incidence of peritoneal seedlings. Residing in rural areas and having a low income, people at risk of this type of cancer generally seek medical advice only at a late stage of the disease.

This fact, plus ignorance about the latent interval for the bile duct epithelium to undergo malignant change, makes any screening programme likely to be ineffective. Consequently, at present there is no screening programme for cholangiocarcinoma in patients with opisthorchiasis in Thailand. Although aggressive surgery has been recommended by several centres, its role in patients with opisthorchiasis seems less clear cut than in those with classical proximal bile duct cancer. Early lymphatic or systemic metastasis, a high risk of developing multiple intrahepatic bile duct cancer[21] and a tendency to resume the habit of eating raw fish are the underlying reasons. Whenever possible, however, tumour resection is still the firm policy for treating such patients unless there is clear evidence of advanced disease, since survival is better after resection than following bypass. The results of this series show that most patients presenting with jaundice will have metastatic disease, while tumour resection is more likely to be feasible among anicteric patients.

Debris (and sometimes flukes) is usually found in the bile of patients with opisthorchiasis. Relieving the jaundice by either percutaneous transhepatic biliary drainage or placement of a biliary endoprosthesis is therefore rather ineffective. The biliary stent obstructs quite rapidly, leading to cholangitis. Although use of an expandable metal stent may improve the outcome, the treatment is too expensive to apply to most patients with opisthorchiasis, who are typically farmers living in rural areas of the country. The results from this study confirm that, for patients with irresectable tumours, surgical bilioenteric bypass is an effective palliative manoeuvre with acceptable survival and without operative mortality. Whenever possible, segment III duct–enteric bypass should be the procedure of choice, as others have shown[22].

Survival after surgical treatment of hilar cholangiocarcinoma associated with opisthorchiasis in this series is similar to that reported in patients without liver fluke infestation[19,20,22], although lymphatic metastasis is more common. Removal of the tumour, with or without concomitant liver resection, provides significantly better survival than does a palliative procedure.

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British Journal of Surgery 1996, 83, 1065–1070

Surgery for left-sided pancreatic cancer

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A total of 590 exocrine pancreatic cancers of the body or tail of the pancreas, operated on between January 1982 and December 1988, were analysed. There were 128 pancreatic resections (group 1), 164 palliative bypasses (group 2) and 293 exploratory laparotomies which included 74 splanchnicectomies (group 3). The mortality rate was lower in group 1 (9 per cent) than in group 2 (19 per cent) ($P = 0{\cdot}012$). The mortality rate exceeded 40 per cent in groups 1 and 2 for patients aged more than 70 years with pre-existing organ failure. The morbidity rate was 32 per cent in group 1 and 29 per cent in group 2. Patients with metastases had a median survival of 3·4 months, whatever the operative treatment. In the presence of lymph node involvement there was no significant difference in survival between groups 1 and 2. Patients with no metastases and no lymph node involvement had 1- and 3-year survival rates of 38 and 12 per cent respectively after pancreatic resection. Only patients with a small tumour (≤ 4 cm), no lymph node involvement and no metastases achieved a significantly better survival after resection ($P = 0{\cdot}049$). Curative resection should be reserved for a small tumour confined to the pancreas. Fewer than 10 per cent of patients will be suitable for surgery. For the other cases, resection must be considered as a palliative procedure without a significant improvement in survival. It seems justified to limit palliative surgery to candidates for digestive bypass and to use non-surgical palliation for the remainder.

Five-year actuarial survival rates after surgical resection of pancreatic carcinoma range from 5 to 24 per cent[1–7]. Despite these dismal results, surgery remains the gold standard procedure for head pancreatic cancer, associated with a resectability rate of 20 per cent[8,9]. Constant improvement of the postoperative mortality rate from 10 per cent towards zero is a strong argument favouring resection[11–15]. Moreover, in optimal cases with a small tumour (less than 2 cm) confined to the pancreas, without lymph node and vascular involvement, a 5-year actuarial survival rate of 37 per cent has been reported[10]. For cancer of the body or tail of the pancreas, the indication for surgical resection remains questionable, with many published results showing a median survival less than 10 months and a 3-year actuarial survival rate below 10 per cent[16,17].

A retrospective enquiry by the French Association of Surgery collected 590 cancers of the body and tail of the pancreas. Among these cases, 128 patients underwent a pancreatic resection. This paper investigates the factors responsible for the dismal prognosis and attempts to identify suitable indications for surgery in these patients.

Patients and methods

A questionnaire was sent to the members of the Association Française de Chirurgie. Data were collected on a personal computer (PS 2-386, IBM) and analysed by SAS statistical software (SAS Institute, Cary, North Carolina, USA).

The study comprised 3761 patients with histologically proven exocrine pancreatic cancer, operated on between January 1982 and December 1988. Endocrine cancers, cystadenocarcinomas, cancers of the bile duct and the duodenum extending to the pancreas and cancers of the ampulla were excluded. Of 3761 cases, 2942 were located in the head or isthmus of the pancreas, 590 in the body of tail, 215 were diffuse (involving more than two segments), and 14 were undefined. A pancreatic resection was carried out in 787 cases (21 per cent), 128 for body and tail and 659 for head and isthmus cancer.

Table 1 Characteristics of the patients ($n = 590$)

Parameters	n	%
Sex		
Male	383	65
Female	207	35
Age		
≤ 70 years	413	70
> 70 years	177	30
Presenting symptoms		
Pain	512	87
Weight loss	483	82
Diabetes	104	18
Organ failure*		
Yes	111	26
No	321	74
Procedures		
Group 1 (resections)	128	22
Total pancreatectomy	12	
Left pancreatectomy	116	
Group 2 (bypasses)	164	28
Digestive bypass	103	
Biliary and digestive bypass	38	
Biliary bypass	22	
Biliary endoprosthesis	1	
Group 3	293	50
Exploratory laparotomy	219	
Laparotomy + splanchnicectomy	74	
Undefined	5	

*Parameters only available on 432 patients (91 resections, 117 bypasses and 224 laparotomies)

The 590 patients with cancers located in the body or tail of the pancreas (*Table 1*) included 383 men (65 per cent) and 207 women (35 per cent) (M:F = 1·85), with a mean(s.d.) age of 63·5 (10) years. Surgical procedures were: 128 pancreatic resections (22 per cent: group 1) (116 left pancreatectomies and 12 total pancreatectomies); 164 palliative bypasses (28 per cent: group 2); 219 exploratory laparotomies (37 per cent) and 74 laparotomies with splanchnicectomy (12 per cent) (group 3). The procedure was unknown in five cases. Mean age was 61·3 years in group 1, 65·8 years in group 2 and 63 years in group 3 ($P = 0{\cdot}004$).

Paper accepted 1 October 1995

Abdominal pain (87 per cent of cases) and weight loss (82 per cent of cases) were the most frequent presenting symptoms. Preoperative organ failure was noted in 26 per cent of patients, mainly cardiac failure (8 per cent) and respiratory insufficiency (7 per cent).

Postoperative mortality and morbidity rates (≤ 30 days) and late complications were calculated for the overall population, compared specifically between each therapeutic group and according to age of patients, pre-existing organ failure and presence of metastases. Contingency tables were analysed with the χ^2 and Fisher's exact tests. Survival distribution functions were determined by the Kaplan–Meier method and the curves were compared with the log rank test. Only patients who survived more than 30 days were included in the survival analysis.

To determine the factors affecting the prognosis of body and tail cancer compared with that of the head and isthmus after a successful pancreatic resection, univariate and stepwise multivariate regression analyses were performed. The seven factors entered into a Cox model were location of the primary, abdominal pain, weight loss, tumour size, lymph node involvement, adjacent organ involvement and metastases.

Differences in the total number of patients depended on missing data in some questionnaires.

Results

There were 590 patients with cancer of the body and tail of the pancreas.

Resectability

At admission, 359 (61 per cent) patients had metastases, 28 per cent of group 1, 66 per cent of group 2 and 73 per cent of group 3 ($P < 0{\cdot}001$). Metastases were chiefly located in the liver (43 per cent) or the peritoneum (35 per cent), and were significantly more frequent in groups 2 and 3 ($P < 0{\cdot}001$). Eighty-six per cent of patients (361 of 419 available data sets) had a tumour at least 4 cm in diameter, and 14 per cent ($n = 58$) a tumour less than 4 cm in diameter. Group 1 included a significantly higher number of tumours less than 4 cm (29 per cent) in comparison with group 2 (11 per cent), and group 3 (9 per cent) ($P < 0{\cdot}001$). Lymph node involvement was present in 60 per cent of group 1. The resectability rate was 22 per cent ($n = 128$).

The principal contraindications for resection were: presence of metastases (50 per cent), vascular involvement (34 per cent), patient's age and general health status (17 per cent), lymph node involvement (7 per cent), or other causes (15 per cent). Several contraindications were sometimes present in one patient. Most resections ($n = 116$, 91 per cent) consisted of distalpancreatectomy and splenectomy. Gastroenterostomy ($n = 103$) represented 63 per cent of all palliative bypasses. Twenty-eight patients underwent an extended *en bloc* resection including organs other than the pancreas and the spleen, and in seven cases a vascular resection was required. Thirty-six patients in group 1 (28 per cent) underwent a pancreatic resection despite the presence of liver metastases.

Resection was considered to be curative in 49 per cent of cases and palliative in 51 per cent. Adjuvant or complementary treatment using only radiotherapy, only chemotherapy or both was given in 91 cases (15 per cent), 68 cases (12 per cent) and 26 cases (4 per cent).

Adjuvant radiotherapy and chemotherapy consisted of: radiotherapy (2 Gy daily for 5 days) and 5-fluorouracil (5-FU) (25 mg/kg daily for 4 days) the first week, only radiotherapy for the second week, and two weeks without treatment followed by a second similar cycle. Palliative chemotherapy consisted of 5-FU (1 mg/m^2 perfused intravenously for 24 h) from days 1–5 and cisplatinum (100 mg/m^2) on day 2, every 4 weeks.

Operative mortality

The overall postoperative mortality rate was 12 per cent (*Table 2*). Mortality was lower in group 1 (9 per cent) than in group 2 (19 per cent) ($P = 0{\cdot}012$). There was no postoperative death after total pancreatectomy ($n = 12$) and after pancreatic resections with vascular resection ($n = 7$). Age (below or above 70 years) as an isolated factor had no influence on mortality whatever the group. Conversely, the combination of age over 70 years and the presence of one or more organ failures was associated with mortality rates of 40 and 45 per cent in groups 1 and 2 respectively. In group 2, the mortality rate was significantly higher in patients with metastases (22 per cent) and in those with a pre-existing organ failure (38 per cent).

Non-fatal complications

The overall postoperative morbidity rate was 22 per cent (*Table 2*), of which haemorrhage represented 3 per cent, renal failure 1·2 per cent, pancreatic fistula 1 per cent and digestive fistula 0·5 per cent. The rate was higher for patients in group 1, aged less than 70 years ($P < 0{\cdot}001$), without pre-existing organ failure ($P < 0{\cdot}001$). In the presence of metastases, the morbidity rate was higher in

Table 2 Postoperative mortality and morbidity in patients with left-sided pancreatic cancer

	Resection ($n = 128$)	Bypass ($n = 164$)	Laparotomy ($n = 293$)	P*
Mortality	11/128 (9)	31/164 (19)	30/293 (10)	<0·012
Age				
≤70 years	8/102 (8)	16/107 (15)	19/206 (9)	0·209
>70 years	3/26 (12)	15/57 (26)	11/87 (13)	0·081
Organ failure				
Yes	2/29 (7)	11/29 (38)	10/54 (19)	0·010
No	9/99 (9)	20/135 (15)	20/239 (8)	0·162
Metastases				
Yes	4/36 (11)	24/108 (22)	24/215 (11)	0·030
No	7/92 (8)	7/56 (12)	6/78 (8)	0·563
Morbidity	41/128 (32)	48/164 (29)	41/293 (14)	<0·001
Age				
≤70 years	32/102 (31)	28/107 (26)	25/206 (12)	<0·001
>70 years	9/26 (35)	20/57 (35)	16/87 (18)	0·050
Organ failure				
Yes	8/29 (28)	14/29 (48)	14/54 (26)	0·096
No	33/99 (33)	34/135 (25)	27/239 (11)	<0·001
Metastases				
Yes	15/36 (42)	35/108 (32)	29/215 (13)	<0·001
No	26/92 (28)	13/56 (23)	12/78 (15)	0·134
Complications				
Haemorrhage	8/128 (6)	3/164 (2)	7/293 (2)	0·06
Renal insufficiency	1/128 (0·8)	2/164 (1)	4/293 (1)	0·34
Pancreatic fistula	4/128 (3)	1/164 (0·6)	—	0·001
Digestive fistula	1/128 (0·8)	2/164 (1)	—	0·07
Miscellaneous	27/128 (21)	40/164 (24)	30/293 (10)	0·001

Values in parentheses are percentages. *χ^2 test (2 d.f.)

group 1 (42 per cent) than in group 2 (32 per cent) or group 3 (14 per cent) ($P<0{\cdot}001$).

The overall rate of late complications was 30 per cent ($n=178$): 45 per cent ($n=57$) in group 1, 25 per cent ($n=41$) in group 2, 27 per cent ($n=80$) in group 3 ($P<0{\cdot}001$). Diabetes ($P<0{\cdot}001$), hypoglycaemia ($P<0{\cdot}001$) and malabsorption ($P=0{\cdot}015$) were more frequent in group 1 (*Table 3*).

The overall reoperation rate was 10 per cent ($n=61$): 27 per cent ($n=35$) in group 1, 9 per cent ($n=15$) in group 2, 1·3 per cent ($n=4$) in group 3 ($P<0{\cdot}001$). Reoperations after pancreatic resection were performed for haemorrhage ($n=12$), intra-abdominal sepsis ($n=10$), intestinal obstruction ($n=5$), wound abscess ($n=4$), evisceration ($n=2$), digestive fistula ($n=1$) and pancreatic fistula ($n=1$).

Actuarial survival

The overall survival rate was 17 per cent at 1 year, 6·7 per cent at 2 years, 2·9 per cent at 3 years and 1 per cent at 5 years. Median and mean survival were 4·5 and 8·2 months respectively.

Patients with metastases had a median survival of 3·4 months and no significant difference in survival was recorded between the groups (*Fig. 1*). In the absence of metastases the overall median survival was 7 months, longer in group 1 (9·1 months) than in group 2 (6·3 months) ($P=0{\cdot}065$).

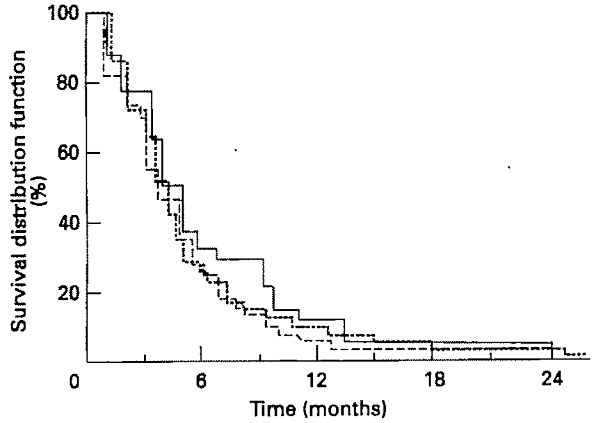
In group 1, patients who had neither metastases nor lymph node involvement ($n=31$) had a median survival of 9·2 months and an actuarial survival rate at 1 year, 2 years and 3 years of 38, 24 and 12 per cent respectively. These patients did slightly but not significantly better than those with lymph node involvement (*Fig. 2*). In the presence of lymph node involvement survival did not differ between the groups (*Fig. 3*).

After total pancreatectomy median survival was 9·2 months with no survivors at 2 years. After extended resection to a vascular structure, median survival was 8·5 months with no patient alive at 2 years.

Table 3 Late complications: comparative study according to the therapeutic groups

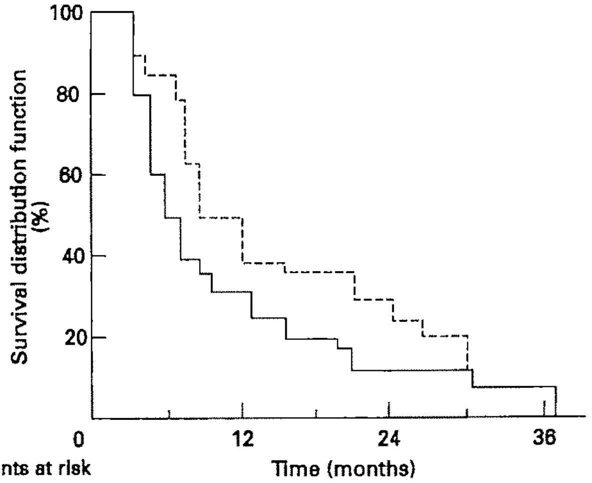
Parameters	Resection ($n=128$)	Bypass ($n=164$)	Laparotomy ($n=293$)	P*
Late complications	57 (45)	41 (25)	80 (27)	<0·001
Jaundice	11 (9)	8 (5)	18 (6)	0·426
Digestive stenosis	7 (5)	9 (5)	18 (6)	0·943
Abdominal pain	32 (25)	24 (15)	65 (22)	0·063
Diabetes	13 (11)†	4 (2)	3 (1)	<0·001
Malabsorption syndrome	6 (5)	7 (4)	2 (1)	0·015
Hypoglycaemia	6 (5)	—	—	<0·001
Others	13 (10)	9 (5)	13 (4)	0·071

Values in parentheses are percentages. *χ^2 test (2 d.f.). †Diabetes following total pancreatectomy was excluded



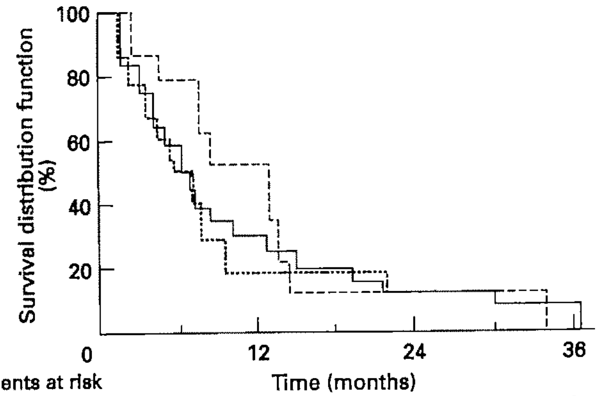
Patients at risk	0	6	12	18	24
Resection	31	10	3	1	–
Bypass	80	15	4	2	2
Laparotomy	177	36	14	6	1

Fig. 1 Actuarial survival of patients with metastases according to therapeutic groups: ——— pancreatic resection (group 1, $n=31$); ––––, palliative bypass (group 2, $n=80$); -----, explorative laparotomy (group 3, $n=177$). $P=0{\cdot}39$ (log rank test)



Patients at risk	0	12	24	36
N–	31	10	5	–
N+	39	8	4	2

Fig. 2 Actuarial survival curves after pancreatic resection (group 1) in patients without metastases, with (N+) or without (N–) lymph node involvement. ———, N+ ($n=39$); ––––, N– ($n=31$); $P=0{\cdot}106$ (log rank test)



Patients at risk	0	12	24	36
Resection	39	8	4	2
Bypass	10	3	1	–
Laparotomy	14	1	–	–

Fig. 3 Actuarial survival curves after: ——— pancreatic resection (group 1, $n=39$); –––– bypass (group 2, $n=10$); and ----, exploratory laparotomy (group 3, $n=14$) in patients without metastases but with lymph node involvement. $P=0{\cdot}663$ (log rank test)

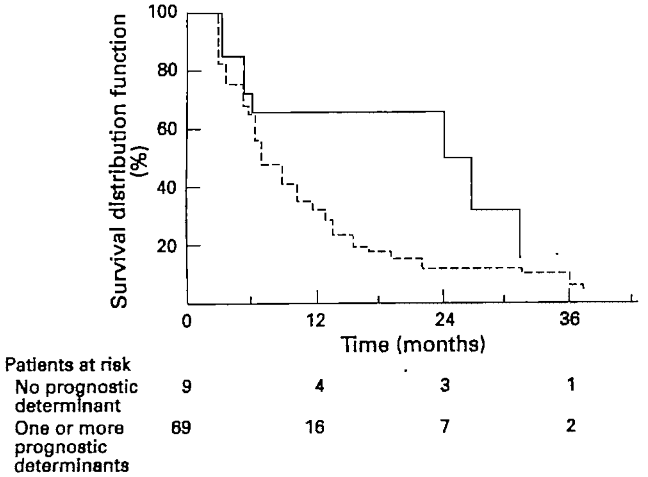


Fig. 4 Actuarial survival curves after pancreatic resection in (———) patients without any adverse prognostic feature (small tumour ≤4 cm, no lymph node involvement, no metastasis) *versus* the remainder (––––). $P = 0{\cdot}049$ (log rank test)

Only patients with a small tumour (≤4 cm), no lymph node involvement and no metastases had a significantly better survival rate after resection than the remainder (*Fig. 4*).

Comparison of cancer of the pancreatic head and isthmus and of the body and tail

Univariate analysis. Median survival after pancreatic resection was always significantly lower for cancers of the body or tail of the pancreas than for head or isthmus cancers when each prognostic feature was tested separately (*Table 4*).

Multivariate analysis.. Four factors proved independently significant in multivariate analysis: adjacent organ involvement ($P = 0{\cdot}0001$), lymph node involvement ($P = 0{\cdot}0001$), metastasis ($P = 0{\cdot}0007$) and the size of the primary tumour ($P = 0{\cdot}0114$). The location of the primary tumour failed to achieve statistical significance in multivariate analysis. Body and tail cancers were significantly associated with a higher frequency of these prognostic determinants ($P = 0{\cdot}0001$, *Table 5*).

Table 5 Distribution of the frequency of the prognostic determinants recorded according to location of the primary

	Tumour site	
No. of prognostic determinants	Head and isthmus (%)	Body and tail (%)
0	26·9	11·5
1	42·0	23
2	24·5	38·4
3	6·1	16·6
4	0·2	10·2
Total	100	100

Discussion

To the authors' knowledge this multicentre retrospective trial has collected the largest reported number of pancreatic cancers located in the body and tail, treated by surgical resection ($n = 128$). The potential disadvantages of retrospective data collection are outweighed by the large numbers reported, and by the use of hard outcome data such as actual survival.

The rate of resectability in this location reported in the literature is less than 15 per cent, and to a great extent explains the short series published[17–21]. In this study the resection rate was 22 per cent, but 36 patients underwent resection despite the presence of metastases and only patients who underwent operation were included. Excluding patients with metastases, the corrected rate of resectability was 16 per cent, which was comparable to previous studies.

Table 4 Univariate analysis: mean and median survival (months) after resection of cancer of the pancreatic head and isthmus and of the body and tail related to different prognostic determinants (operative mortality excluded)

	Head and isthmus			Body and tail			
Parameters	($n = 574$)*	Median survival	Mean(s.e.m.)	($n = 110$)*	Median survival	Mean(s.e.m.)	*P*†
Abdominal pain							
No	298 (52)	15·1	24·1(1·5)	12 (11)	5·9	9·3(2·1)	0·009
Yes	276 (48)	13·1	19·0(1·0)	98 (89)	6·7	11·1(1·1)	<0·001
Weight loss							
No	178 (31)	15·8	24·1(1·8)	26 (24)	6·7	10·8(1·8)	0·003
Yes	396 (69)	13·2	22·3(1·2)	84 (76)	6·8	10·6(1·1)	<0·001
Tumour size							
≥4 cm	150 (36)	11·1	17·5(1·4)	74 (67)	6·7	10·8(1·4)	0·009
<4 cm	262 (64)	15·5	25·8(1·6)	36 (33)	10·5	16·1(2·6)	0·215
Lymph node involvement							
No	253 (49)	18·4	29·4(1·7)	43 (39)	9·1	13·1(1·7)	0·001
Yes	259 (51)	11·1	16·8(1·2)	67 (61)	5·2	9·4(1·3)	<0·001
Metastases							
No	556 (97)	14·3	23·5(1·1)	79 (72)	9·1	12·9(1·3)	<0·001
Yes	18 (3)	7·3	12·3(3·1)	31 (28)	4·5	6·3(1·0)	0·061
Adjacent organ involvement							
No	303 (74)	16·6	25·0(1·5)	75 (68)	12·6	15·7(2·0)	0·303
Yes	109 (26)	8·2	17·1(2·0)	35 (32)	6·7	10·0(1·5)	0·020
No prognostic determinant	88	24·9	28·2(2·0)	9	25·2	20(4·3)	0·508

*Values in parentheses are percentages. †Comparison of survival, log rank test

The contraindications for resection were metastases in half the cases and in one-third of cases were local extension of the tumour to adjacent vessels or organs[16,21]. Delayed diagnosis is an attribute of pancreatic cancer of the body or tail. In one series the diagnosis was made in 15 per cent of patients when an abdominal mass was palpable[16].

In the present multivariate analysis four independent parameters influenced survival: adjacent organ involvement, lymph node involvement, metastases, size of the tumour. The location of the tumour had no influence on survival. Conversely, it was seen that body and tail cancers were associated with a higher frequency of prognostic determinants than head and isthmus cancer. This suggests that the dismal prognosis of cancer of the body and tail may be directly linked to the number of adverse prognostic features, which result from a delayed diagnosis rather than a specific gravity *per se*. The fact that median survival was similar for patients without any adverse prognostic feature and whatever the location of the tumour supports this hypothesis.

In this study, overall median and mean survival rates were 4·5 and 8·2 months respectively with a 3-year survival rate of 3 per cent. On the basis of similar results, some authors concluded that left-sided pancreatic cancer was 'virtually incurable and resection should be always considered as a palliative procedure'[22,23]. Conversely, some rare cases of long-term survival (more than 5 years) have been reported after surgical resection[16,23–25]. One objective of the present study was to define clearly which patients could benefit from resection.

The rate of mortality was significantly higher after palliative bypass than after resection, particularly for patients with metastases and those with preoperative organ failure. In a review of the literature Watanapa and Williamson reported similar findings of 14 per cent mortality rate after palliative surgery and 9 per cent after resection[22]. Age as an isolated factor did not influence mortality but did so when associated with organ failure. This concept has already been noted after pancreaticoduodenectomy[2,6,15,26,27]. In the multicentre study of Bakkevold *et al.*[14], mortality after resection was only influenced by the Karnofsky score, whereas two other variables (presence of metastases and diabetes) became significant after palliative bypass. Since the median survival in patients with metastases is 3·4 months whatever the surgical procedure, a pancreatic resection is not indicated in these patients, and a palliative bypass is often superfluous.

What are the reasonable limits of resectability in localized cancer? Johnson *et al*[19]. reported no patient surviving beyond the first year after operation when the primary tumour involved the portal vein, requiring resection of the vein with interposition of a vascular graft. The same authors suggested that occlusion of splenic vessels was not an absolute contraindication to resection but often reflected invasive tumour associated with early recurrence and poor survival[19]. In the present study, except for two patients, survival was not seen beyond 1 year after total pancreatectomy or pancreatectomy with vascular resection. Dalton *et al.*[16] demonstrated that extensive resection for tumours involving adjacent organs was followed by a high rate of recurrence (78 per cent), an increase in hospital stay and produced a modest gain in survival. Only two of 28 patients in the present series survived more than 2 years after extended resection, but the operative mortality and morbidity rates were 14 and 46 per cent. For an irresectable extended tumour, numerous adjuvant therapies have been assessed. The benefit of those therapies remains questionable in view of the modest gain of life achieved.

In the absence of metastases but with lymph node involvement, no difference in survival was seen after either a resection or a bypass. Nevertheless it seems that resection should be proposed for tumour confined to the pancreas even with proximal lymph node involvement in healthy patients. However, these resections should be considered to be palliative.

In this study only nine patients with a small tumour (less than 4 cm) and no lymph node involvement significantly benefited from pancreatic resection. In such optimal cases, the median survival of 25 months was comparable to that obtained after resection of tumours of the head and isthmus tumour.

Curative resection for pancreatic cancer of the body or tail should only be performed for those rare, small tumours not extending outside the pancreas. Even with these optimal indications, probably only 5–10 per cent of patients will be suitable for surgery. For the others, even if surgical resection is feasible, it should always be considered as a palliative procedure without any significant improvement in survival. In that case surgery should be limited to candidates for a necessary digestive bypass. Palliative procedures should be associated with an intraöperative chemical splanchnicectomy to reduce pain in symptomatic patients and to prevent onset of pain in asymptomatic patients[28]. All other patients will obtain equal benefit from non-surgical palliation for pain relief.

Acknowledgements

The authors thank the surgeons of the Association Française de Chirurgie for help in transmitting their records. This study was supported by a grant from the Association Française de Gastroenterologie.

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British Journal of Surgery 1996, 83, 1071–1075

Proinflammatory cytokine release by peripheral blood mononuclear cells from patients with acute pancreatitis

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Proinflammatory cytokine release was measured from peripheral blood mononuclear cells (PBMCs) isolated from six volunteers and, on admission, from 16 patients with acute pancreatitis. Tumour necrosis factor (TNF) release in patients did not differ significantly from that of volunteers, whereas both interleukin (IL) 6 and IL-8 release in patients was raised when compared with that in the volunteer group (mean(s.e.m.) IL-6 20·7(4·6) *versus* 9·3(1·7) ng/ml, $P = 0·03$; IL-8 283(40) *versus* 128(22) ng/ml, $P = 0·04$). When variation in white cell count was accounted for, IL-6 and IL-8 release but not that of TNF was significantly greater in patients with severe disease than in those with mild disease. These results point to a complex upregulation of proinflammatory cytokine release from PBMCs in patients with acute pancreatitis, components of which relate to the clinical progress of the disease.

Acute pancreatitis is a common and potentially fatal disease which is characterized by a systemic inflammatory response that may progress to multiple organ failure and death. It has been proposed[1] that organ dysfunction results from excessive leucocyte activation. Barie and co-workers[2] have noted that the pulmonary sequelae of experimental acute pancreatitis in sheep are prevented by leucocyte depletion before the induction of pancreatitis. Similarly leucocyte depletion reduces acute lung injury in experimental acute pancreatitis in rats[3]. In other models of pancreatitis, pronounced margination of leucocytes within the capillaries and venules of the liver and lungs is an early event in progressive organ dysfunction and failure[4]. Research has focused on neutrophil activity, but other cellular systems may be important in pathogenesis of the disease. The mechanisms promoting intravascular leucocyte activation are not clear. Proinflammatory mediators may be released into the circulation from the focus of the acutely inflamed pancreas. Endotoxaemia is a recognized feature of the disease[5] and may also mediate intravascular events.

The evidence for leucocyte activation in acute pancreatitis in humans has largely been accrued through indirect means by measurement of surrogate markers of inflammation in the serum of patients. Neutrophil elastase released during phagocytosis is rapidly complexed in the circulation with α_1-protease inhibitor. The serum concentration of this complex is raised in a number of inflammatory conditions, including acute pancreatitis[6], and is thought to be a crude marker of neutrophil activation. Other leucocyte products, including proinflammatory cytokines such as tumour necrosis factor (TNF) and interleukin (IL) 6, have been measured in patients with acute pancreatitis. TNF is a short-lived cytokine, produced early in the disease process, and is thus often undetectable in the serum of patients following admission[6]. However, the level of IL-6 appears to be more stable and is raised in the serum of patients with acute pancreatitis, correlating to some degree with the severity of disease[7,8].

This paper investigates whether *in vitro* proinflammatory cytokine release by peripheral blood mononuclear cells (PBMCs) is associated with disease severity *in vivo*. To examine leucocyte activation directly, the study investigated the spontaneous and endotoxin-stimulated release of proinflammatory cytokines from PBMCs isolated from patients with acute pancreatitis. Cytokine release *in vitro* was then related to the clinical course of the patients and to the serum concentration of the corresponding cytokine. To investigate the influence of serum factors on cytokine release, PMBCs were incubated in both autologous serum and fetal calf serum (FCS). PBMCs are a mixed cell population comprised largely of monocytes and lymphocytes. These cell types participate in intercellular signalling which can significantly modify cell function in mixed cultures in comparison with that in monocultures of cells[9]. Thus coincubation of mononuclear cells is important as it may more accurately reflect their actions *in vivo*.

Patients and methods

Sixteen consecutive patients with acute pancreatitis were studied. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical or radiographic evidence accompanied by a serum amylase concentration greater than 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; normal range 70–300 units/l). Peripheral blood was taken from patients on the first day of admission for isolation of PBMCs, acquisition of serum and white cell counting. The progress of the patient was evaluated with regard to the development of pancreatic complications as defined by the 1992 Atlanta Convention[10] or of multiple organ failure as defined by the Goris score[11]. No patient was receiving steroids, non-steroidal anti-inflammatory drugs or other immunosuppressive medication on admission. Six control subjects were healthy volunteers, taking no medication and with no known pancreatic pathology. Written informed consent was obtained from patients and the protocol was approved by the local ethics committee.

Isolation and culture of peripheral blood mononuclear cells

PBMCs were cultured in 96-well flat-bottomed tissue culture plates at 2×10^5 cells per well in 200 μl RPMI 1640 supplemented with penicillin 50 units/ml, streptomycin 50 μg/ml, glutamine 2 mmol/l and 5 per cent FCS (ICN Flow Laboratories, Irvine, UK) or 5 per cent autologous serum. In lipopolysaccharide (LPS)-stimulated cultures (*Escherichia coli* 0127:B9; Sigma Chemicals, Poole, UK) the final concentration of LPS was

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5 μg/ml. Supernatants from the cultures were removed after 24 h and stored at −70°C for subsequent batch cytokine assay. All cultures were performed at 37°C in the presence of 5 per cent carbon dioxide.

Assay for interleukins 6 and 8 and tumour necrosis factor

IL-6, IL-8 and TNF were measured by enzyme-linked immunosorbent assay (ELISA). The capture antibody was mouse monoclonal anti-human IL-6 antibody (Boehringer Mannheim, Lewes, UK) or rabbit polyclonal anti-human IL-8 (AMS Biotechnology UK, Witney, UK). The detecting antibodies were goat polyclonal anti-IL-6 or anti-IL-8 antibody (R&D Systems, Oxon, UK) followed by polyclonal sheep anti-goat immunoglobulin G horseradish peroxidase-labelled antibody (Sigma Immunochemicals, Poole, UK) with tetramethylbenzidine (Boehringer Mannheim) as substrate. The limits of sensitivity of the assays were 40 pg/ml for IL-6 and 200 pg/ml for IL-8. Intra-assay and interassay variation was less than 5 per cent. The capture antibody for TNF was mouse monoclonal anti-human TNF and the detecting antibody was peroxidase-conjugated mouse monoclonal anti-human TNF Fab fragments (Boehringer Mannheim), used according to the manufacturer's instructions. The limit of sensitivity of the assay was 15 pg/ml. Intra-assay and interassay variation was less than 4 per cent.

Statistical analysis

Comparison between patient and control groups or between those with mild and severe disease was performed with the Mann–Whitney U test. Comparison within patient or control groups was made with the paired Student's t test. $P<0{\cdot}05$ was considered significant.

Results

There was no significant difference in the mean (range) age between patients with acute pancreatitis and controls, (55·8 (23–96) *versus* 47·5 (26–73) years respectively, ($P=0{\cdot}41$)) with a 1:1 sex ratio in both groups. Five of the 16 patients were considered to have severe disease: two with pancreatic necrosis and three with renal impairment on admission (scoring 1 on the Goris score for the renal system with a serum creatinine level greater than 170 μmol/l), which returned to normal limits with conservative therapy.

The mean spontaneous and LPS-stimulated TNF release from PBMCs of patients with acute pancreatitis, whether incubated in FCS or autologous serum, was similar to that of the control group (*Table 1*). In contrast, the mean spontaneous IL-6 release from PBMCs was significantly increased in the pancreatitis group compared with that in controls when cultured in autologous serum, but this effect was not seen when the cells were cultured in FCS (*Table 1*). The mean LPS-stimulated IL-6 release from PBMCs was significantly increased in the patient group compared with that in the control group when cultured with either FCS or autologous serum (*Table 1*). The mean spontaneous and LPS-stimulated release of IL-8 from PBMCs was significantly increased in patients with pancreatitis compared with that in controls, with the effect seen whether the cells were incubated with FCS or autologous serum (*Table 1*).

The release of TNF, IL-6 and IL-8 from PBMCs isolated from patients with acute pancreatitis and healthy volunteers was significantly increased when the cells were incubated in the presence of LPS in comparison with spontaneous cytokine release (*Table 1*). The mean ratio of LPS-stimulated TNF and IL-6 release to spontaneous cytokine release was not significantly greater in patients with pancreatitis than in controls (3·5 (95 per cent confidence interval (c.i.) 2·4–4·9) *versus* 2·3 (95 per cent c.i. 1·4–3·3) for TNF and 2·8 (1·7–4·0) *versus* 1·7 (1·2–2·5) for IL-6 respectively.

Incubation of PBMCs with autologous serum in comparison with FCS produced a greater mean increase in spontaneous TNF and IL-6 release in patients with pancreatitis compared with controls (ratio for TNF 3·4 (95 per cent c.i. 2·1–5·0) *versus* 1·7 (95 per cent c.i. 1·6–1·9), $P=0{\cdot}01$; IL-6 2·0 (1·6–2·8) *versus* 1·6 (1·4–1·9), $P=0{\cdot}04$). IL-8 release was not significantly enhanced in either the pancreatitis or control group from PBMCs cultured in media supplemented with autologous serum compared with FCS (1·4 (0·9–1·8) *versus* 1·2 (0·8–1·7), $P=0{\cdot}36$).

TNF and IL-6 were detectable on the first day of admission in the serum of seven patients, five of whom developed severe disease as described above (*Fig. 1*). However, there was no correlation between the serum TNF and IL-6 concentration and spontaneous PBMC

Table 1 Spontaneous and lipopolysaccharide-stimulated tumour necrosis factor, interleukin 6 and interleukin 8 release from peripheral blood mononuclear cells isolated from six healthy volunteers and during the first day of admission in 16 patients with acute pancreatitis

Culture condition	TNF (pg/ml)	IL-6 (ng/ml)	IL-8 (ng/ml)
Spontaneous in FCS			
Control	1356(376)	6·9(1·5)	103(17)
Pancreatitis	1339(374)	10·6(1·3)	238(26)*
Spontaneous in AS			
Control	2053(741)	9·3(1·7)	128(22)
Pancreatitis	2425(441)	20·7(4·6)*	283(40)*
LPS stimulation in FCS			
Control	2596(839)	11·5(0·9)	192(20)
Pancreatitis	3554(825)	24·4(2·5)*	427(35)*
LPS stimulation in AS			
Control	3994(1199)	17·7(2·6)	135(16)
Pancreatitis	4799(708)	35·8(5·5)*	419(56)*

Cells were incubated in the presence of 5 per cent fetal calf serum (FCS) or 5 per cent autologous serum (AS). Values are mean(s.e.m.). TNF, tumour necrosis factor; IL, interleukin; LPS, lipopolysaccharide. $*P<0{\cdot}05$ (pancreatitis *versus* control, Mann–Whitney U test)

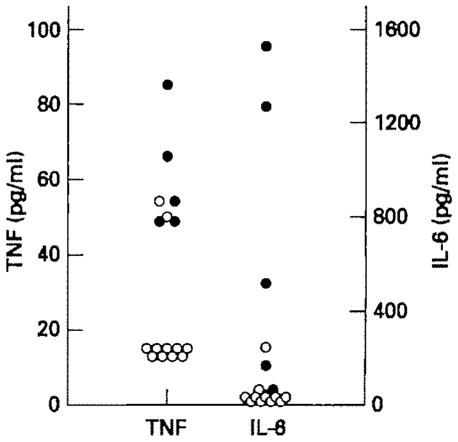

Fig. 1 Serum tumour necrosis factor (TNF) and interleukin (IL) 6 concentration in patients with acute pancreatitis measured on the first day of admission. ●, Patients with severe disease ($n=5$); ○, patients with mild disease ($n=11$)

cytokine release ($r = 0{\cdot}10$, $P = 0{\cdot}71$ and $r = 0{\cdot}22$, $P = 0{\cdot}42$ for TNF and IL-6 respectively). IL-8 was detected in the serum of only two patients. TNF, IL-6 and IL-8 were undetectable in the serum of volunteers.

The spontaneous release of TNF, IL-6 and IL-8 from PBMCs isolated from patients with acute pancreatitis on the first day of admission, and cultured at a standard cell concentration of 10^6 per ml, is depicted in *Fig. 2*. PBMC release of TNF, IL-6 and IL-8 was not significantly different between the 11 patients with mild and the five with severe pancreatitis. As an estimation of cytokine production per unit of blood, allowing for the variation in white cell count between patients, cytokine production from the standard cell concentration was multiplied by the mononuclear cell count (monocyte count plus lymphocyte count) measured on the first day of admission; these results are depicted in *Fig. 3*. PBMC IL-6 and IL-8 release

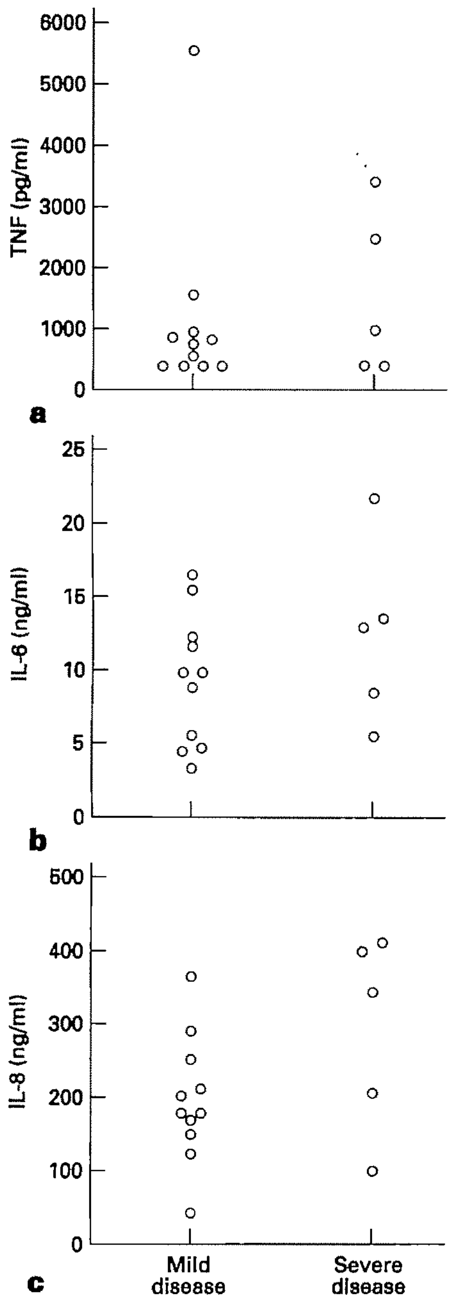

Fig. 2 Spontaneous release of a tumour necrosis factor (TNF), b interleukin (IL) 6 and c IL-8 from peripheral blood mononuclear cells (PBMCs) in patients with acute pancreatitis on the first day of admission, comparing patients with severe disease ($n = 5$) with those with mild disease ($n = 11$). Points represent cytokine release from PBMCs plated at a standard concentration of 10^6 cells/ml. There were no significant differences between patients with mild and severe disease

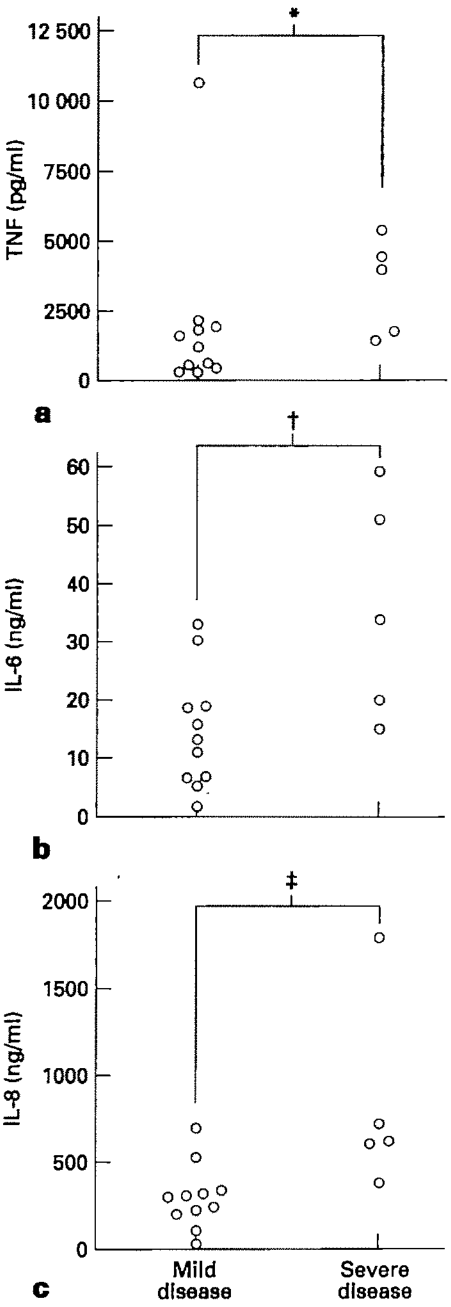

Fig. 3 Spontaneous release of a tumour necrosis factor (TNF), b interleukin (IL) 6 and c IL-8 from peripheral blood mononuclear cells in patients with acute pancreatitis on the first day of admission, comparing patients with severe disease ($n = 5$) with those with mild disease ($n = 11$). Points represent cytokine release from the standard cell concentration multiplied by the white cell count. *$P = 0{\cdot}13$, †$P = 0{\cdot}04$, ‡$P = 0{\cdot}02$ (Mann–Whitney *U* test)

per unit of blood in patients with severe disease was significantly increased compared with that in mild disease. However, there was no significant difference in TNF release from PBMCs between the two groups (*Fig. 3*).

Discussion

This study demonstrates increased release of IL-6 and IL-8 from PBMCs in the blood of patients with acute pancreatitis compared with that in healthy volunteers (*Table 1*). While there was no significant difference in proinflammatory cytokine release per cell when comparing patients with mild or severe disease (*Fig. 2*), making allowance for the white cell count revealed that IL-6 and IL-8 release per unit of blood was significantly greater in those with severe disease (*Fig. 3*). This effect was not observed for TNF release (*Fig. 3*) despite the observation that TNF plays an important early role in the cascade of inflammatory events[12]. Although blood was withdrawn from patients as soon after admission as feasible, the disease process, as manifested by patient symptoms, had been present for hours and in some cases days before admission. It is thus likely that significant release of TNF from PBMCs had already occurred, as indicated by raised serum TNF levels in a number of patients (*Fig. 1*). It is perhaps of greater significance, with regard to the pathogenesis of acute pancreatitis and its complications, that PBMCs in patients were still able to mount a similar TNF response to that in healthy volunteers despite the raised serum TNF concentration.

Endotoxaemia is a feature of acute pancreatitis. Foulis and co-workers[5] detected endotoxin in the serum of 13 of 26 patients with acute pancreatitis. More recently a significant fall in the serum levels of endogenous anti-endotoxin core antibodies was observed in 28 of 33 cases, implying exposure to endotoxin[13]. Monocyte activation follows exposure to bacterial LPS. While monocytes are able to recognize LPS directly[14], activation is potentiated when LPS forms a complex with LPS binding protein, which then interacts with the monocyte CD14 receptor[15]. LPS binding protein is present in human serum but, being an acute-phase protein, its serum concentration is raised in patients with acute pancreatitis. The concentration of LPS binding protein in FCS is not known. However, the presence of LPS binding protein is a consistent finding in other animals[16] and its presence in FCS is probable. In the present study incubation with endotoxin led to an increased release of TNF, IL-6 and IL-8 from PBMCs in both patient and control groups. While endotoxaemia is unlikely to be the primary event in the pathogenesis of acute pancreatitis, its presence could contribute to the state of monocyte activation and subsequent development of the systemic inflammatory response syndrome associated with the disease.

Culture of isolated PBMCs in either autologous serum or FCS allows comparison between the behaviour of cells under the same conditions (FCS) or in the conditions prevailing *in vivo* (autologous serum). Spontaneous TNF and IL-6 release from PBMCs in patients with acute pancreatitis was greater in response to incubation with autologous serum than with FCS. This finding suggests that circulating factors in the serum of patients with acute pancreatitis contribute to the state of PBMC activation with regard to TNF and IL-6 secretion. Damaged acinar cells and the leucocyte infiltrate associated with pancreatitis are known to secrete a wide variety of proinflammatory agents, including complement factors, oxygen-derived free radicals, cytokines, platelet activating factor and leukotrienes[1]. All these agents affect endothelial cells and promote circulating leucocyte activation. Differences in endotoxin concentration between FCS and autologous serum are unlikely to account for this observation, as the LPS stimulation concentration used in this study induced maximal cytokine release in preliminary studies.

An increase in serum IL-6 concentration early in the course of acute pancreatitis is well documented[8,9]. While a number of immunocompetent cells secrete IL-6 *in vivo*, the increased secretion of IL-6 by PBMCs observed in the present patients may contribute significantly to raised serum IL-6 concentrations. Studies have reported that both the concentration on admission and the peak level of serum IL-6 correlate with disease severity[8,9]. Faist *et al.*[17] have shown that monocyte IL-6 secretion is increased twofold in patients with sepsis. In an intervention study using a mouse burn–sepsis model, IL-1β and indomethacin administration reduced the production of TNF, IL-1 and IL-6 by cultured splenocytes towards normal control levels with a corresponding improvement in the survival rate[18]. These results suggest that in inflammatory conditions such as acute pancreatitis excessive production of IL-6 from PBMCs may be altered by therapeutic intervention and could conceivably influence outcome. Alternatively, IL-6 may simply be a marker of more important proinflammatory mediators.

IL-8 was detected in the serum on the first day of admission in only two patients in the present study. The IL-8 ELISA detection limit of 200 pg/ml and the blood's capacity for inactivating IL-8 (principally by means of irreversible binding with red blood cells)[19] render serum IL-8 measurement early in the course of an acute inflammatory disease a poor reflection of cellular or PBMC IL-8 production. Similar upregulation of IL-8 release from monocytes has been observed in a study simulating ischaemia–reperfusion[20]. The role of IL-8 in neutrophil–endothelial cell interaction, through chemoattraction and potentiation of the action of the intercellular adhesion molecule 1 on endothelial cells, is well known[21,22]. In addition IL-8 can induce neutrophil shape change and the shedding of L-selectin from the neutrophil surface, events that appear essential for neutrophil migration[22–24]. However, the role of IL-8 in the propagation of multiple organ failure is not clear. Both Rot[22] and Tanaka *et al.*[25] independently proposed that bloodborne IL-8 can result in premature activation of circulating neutrophils, including the release of L-selectin and activation of the integrin CD11–CD18 ligand. These events serve to prevent neutrophil emigration by inducing intravascular neutrophil aggregation and stiffening of the cell membrane. These prematurely activated neutrophils are carried in the circulation to sequester in the next microcirculation they encounter[26]. This sequence of events would account for the leucocyte sequestration in pulmonary capillaries observed in animal models of acute pancreatitis[27] and for the beneficial effect of leucocyte depletion in preventing pulmonary complications in such models[2,3].

The results of the present study reveal increased proinflammatory cytokine release from PBMCs in patients with acute pancreatitis early in the course of the disease. Further research is required to identify whether this upregulation results from an imbalance in the production of inflammatory mediators or a loss of sensitivity to downregulatory signals, and to determine whether early therapeutic intervention can alter the progress of the disease.

Acknowledgements

This study was supported by the Sir Stanley and Lady Davidson Medical Research Fund and by the Leverhulme Trust.

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British Journal of Surgery 1996, **83**, 1076–1081

Complete resection of the caudate lobe of the liver: technique and results

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The caudate lobe of the liver is a frequent site of involvement by metastatic or primary liver tumours. This study describes the surgical anatomy and analyses the operative technique, results and postoperative morbidity of complete caudate lobectomy. The data represent a retrospective review of 21 consecutive complete caudate lobe resections performed over a 30-month period. The most common diagnosis was metastatic colorectal cancer (nine patients) and the most common procedure was extended left hepatic lobectomy with *en bloc* caudate lobectomy. Four patients underwent isolated complete caudate lobe resection. The median operating time was 5 h and the median blood loss was 1160 ml. The major complication rate was 38 per cent (nine major complications in eight patients) with 10 per cent mortality rate (two deaths). The median hospital stay was 11 days. This series demonstrates the feasibility of routine complete caudate lobe resection for tumours with general principles of liver resection. Isolated caudate lobectomy can be performed safely and the addition of caudate lobectomy to major liver resection does not add significantly to the morbidity or mortality of the procedure.

The caudate lobe of the liver is a frequent site of involvement by both primary[1] and secondary[2,3] liver tumours. In addition, cholangiocarcinoma at the confluence of the bile duct frequently involves caudate bile ducts and may also extend to the caudate lobe[4]. Resection of the caudate lobe of the liver is thus often necessary for complete clearance of tumour during hepatic resection; the procedure may be required as isolated caudate lobe resection or as caudate resection combined with major hepatectomy.

The anatomy of the caudate lobe and its close proximity to major vascular structures make resection difficult and, although there is an increasing number of caudate lobe resections reported in the literature, most are case reports or small series. Furthermore, most series include few complete caudate lobectomies[2,3,5–11] or include only resection for microscopic involvement by cholangiocarcinoma[4].

A variety of techniques has been suggested for resection of the caudate lobe. This communication reviews the anatomy of the caudate lobe and reports technique and results of resection in a series of 21 consecutive complete caudate lobectomies performed over a 30-month period.

Patients and methods

Anatomy

Descriptions of liver anatomy[12–14] rely heavily on the work of Couinaud[15]. The caudate lobe (segment I) is the dorsal portion of the liver lying posteriorly and embracing the retrohepatic inferior vena cava (IVC). It should be clearly appreciated that the lobe lies between major vascular structures: the IVC posteriorly and the portal triad inferiorly, and the IVC and the middle and left hepatic veins at the upper part (*Figs 1* and *2*). The main bulk of the lobe lies to the left of the vena cava, the left and inferior margins being free in the lesser omental bursa. The gastrohepatic omentum separates the left portion of the caudate lobe from segments II and III of the left liver as it passes between them to be attached to the ligamentum venosum. The left portion of the caudate lobe inferiorly traverses to the right between the portal vein and IVC as the caudate process where it fuses with the right lobe of the liver. Superiorly the left portion of the caudate lobe is linked to the posterior margin of the hilum by a deep anterior portion which is embedded in the parenchyma immediately under the middle hepatic veins and fuses on the right side to segments VI and VII of the right liver anterolaterally to the IVC. The portion of the caudate lobe on the right is variable but is usually quite small. The anterior surface within the parenchyma is covered by the posterior surface of segment IV, the limit being an oblique plane slanting from the left portal vein to the left hepatic vein. Thus, there is a caudate lobe (segment I) with a constantly present left portion and a right portion of variable size (*Figs 1* and *2*).

The caudate lobe is supplied by blood vessels and drained by biliary tributaries of the right and left portal triad, but the major blood supply arises from the left branch of the portal vein and the left hepatic artery close to the base of the umbilical fissure of the liver (*Figs 1* and *2*). Small vessels from the portal vein and tributaries joining the bile ducts are also present, usually two on the left side and one on the right. The right portion of the caudate lobe including the caudate process receives predominantly portal venous blood from the right portal vein or the bifurcation of the main portal vein, whereas on the left side the portal supply arises almost exclusively from the left branch of the portal vein. Similarly, the arterial supply and biliary drainage of the right segment is most commonly associated with the right posterior sectoral vessels or pedicle and that of the left segment is associated with the left main vessels[13].

The hepatic venous drainage of the caudate lobe is unique in that it is the only hepatic segment which drains directly into the IVC. The number of hepatic veins is variable (1–9, mean 4)[14]. In general, they are short and drain from the caudate lobe directly into the anterior and left aspect of the vena cava (*Fig. 1*) but they can drain into the posterior aspect of the vena cava if there is a significant retrocaval caudate component.

Usually the posterior edge of the caudate lobe on the left has a fibrous component which fans out to attach to the crus of the diaphragm and extends posteriorly behind the vena cava to link with a similar component of fibrous tissue protruding from the posterior surface of segment VII and embracing the vena cava (*Fig. 1*). It is important to note that in up to 50 per cent of patients this ligament is replaced, in whole or in part, by hepatic tissue and the caudate may thus completely encircle the IVC and contact segment VII on the right side. A significant retrocaval

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Paper accepted 11 April 1996

component may prevent a left-sided approach to the caudate vein. The caudal margin of the caudate lobe has a papillary process which on occasion may attach to the rest of the lobe via a narrow connection. It is bulky in 27 per cent of cases and can be mistaken for an enlarged lymph node on computed tomography[16].

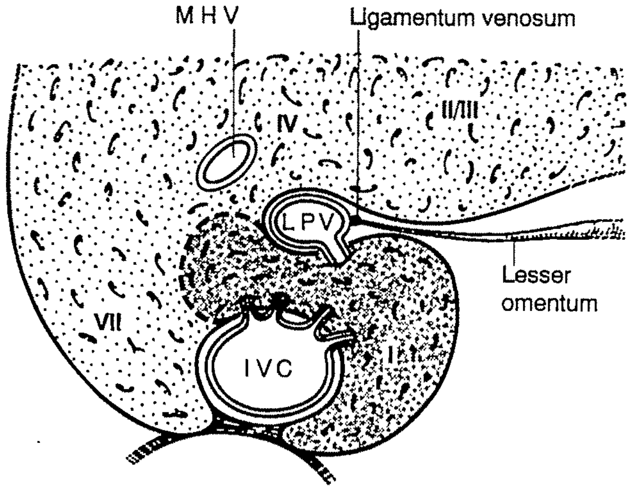

Fig. 1 Cross-sectional sketch showing caudate lobe anatomy at the level of the portal hepatis. LPV, left portal vein, note principal caudate branch; IVC, inferior vena cava; MHV, middle hepatic vein. Note: (1) position of lesser omentum and ligamentum venosum; (2) MHV separates segments IV and V and is close to right portion of caudate lobe; and (3) posterior ligamentous band joining segments I and VII

Resection

The general techniques of major liver resection used in this series have been previously published[17,18]. The lesser omentum is incised and the caudate lobe inspected; a finger is introduced into the lesser sac to palpate the lobe. The operation is carried out with a controlled central venous pressure which is not allowed to rise above 5 mmHg and dissection is performed with the patient in a 15° Trendelenburg position to minimize the possibility of air embolism. Intraoperative ultrasonography is employed routinely to screen the liver for previously undetected metastases and to define the hepatic anatomy in relation to the tumour. On intraoperative ultrasonography the left part of the caudate lobe is clearly demonstrated lying posteriorly to the gastrohepatic (lesser) omentum, whereas the portion in front of and just to the right of the IVC lies posterior to the middle hepatic vein between it and the portal vein. Ultrasonography was not used to guide the plane of parenchymal transection.

The major problems in caudate lobe resection are in dissection and control of the retrohepatic caudate veins and anteriorly, in the presence of a substantial tumour, in controlling bleeding from the middle hepatic vein.

Resection of the caudate lobe involves three major steps: (1) control of the inflow caudate blood supply from the left portal vein and left hepatic artery at the base of the umbilical fissure and from other inflow by lowering of the hilar plate and dividing any vessels encountered; (2) dissection of the retrohepatic veins; and (3) in isolated caudate resection it is necessary to divide the liver parenchyma between the base of segment IV and the left side of segment VII to allow removal of the lobe.

During isolation of the blood supply and bile ducts to the caudate lobe, the first and essential step is to lower the hilar plate[19] so as to display caudate branches. Dissection of the caudate blood supply at the base of the umbilical fissure is usually easy, the caudate vessels being identified issuing from the left side of the portal vein and the left hepatic artery before these vascular structures enter the umbilical fissure (*Figs* 2 and

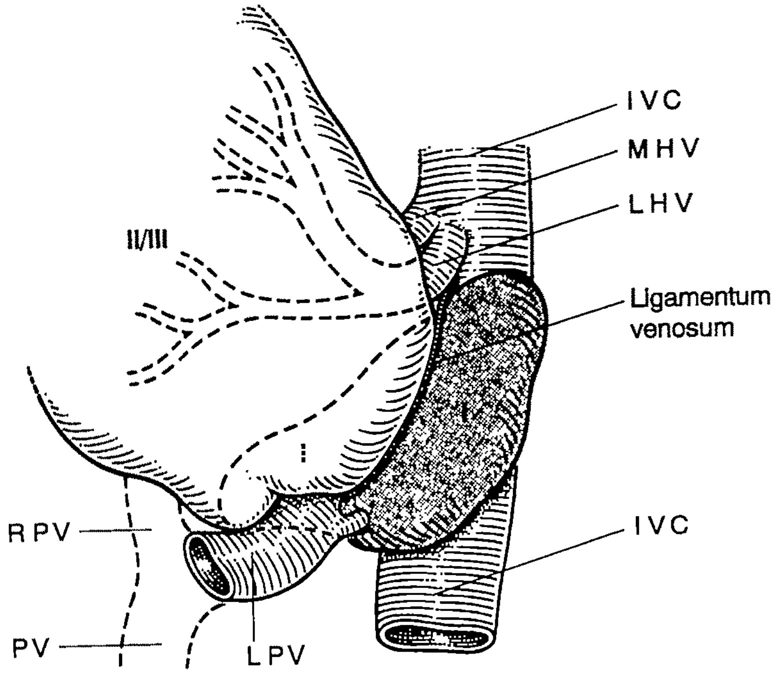

Fig. 2 Sketch showing the position of the caudate lobe relative to surrounding structures and particularly the vena cava. Note segments II and III have been rotated to the right to expose the caudate lobe. The position of the ligamentum venosum is indicated. Note the extension of the caudate lobe between the vena cava and the portal vein anteriorly, and between the vena cava and the middle and left hepatic veins superiorly. Caudate portal blood supply is via a branch of the left portal vein. IVC, inferior vena cava; MHV, middle hepatic vein; LHV, left hepatic vein; LPV, left portal vein; RPV, right portal vein; PV, portal vein

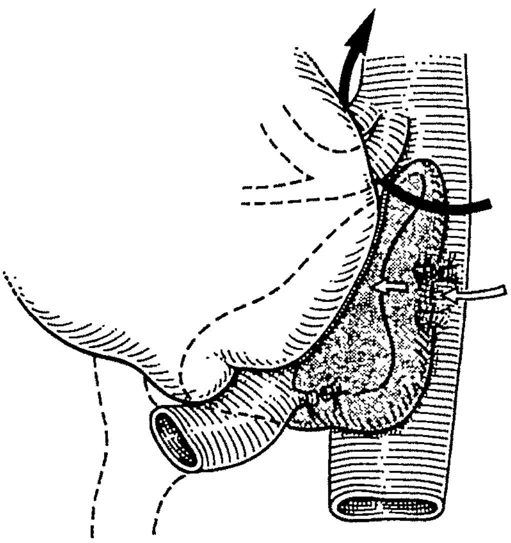

Fig. 3 Start of mobilization of the caudate lobe from the left. The caudate branch of the portal vein has been tied. The caudate lobe has been freed from the left side of the inferior vena cava (IVC) and turned medially (small white arrow). Dissection is proceeding between the vena cava and the caudate lobe (large white arrow). The retrocaudate hepatic veins are being tied. The black arrow indicates the tunnel between the middle and left hepatic veins and the IVC. Dissection of this tunnel allows placement of a clamp across the left and middle hepatic veins (see text)

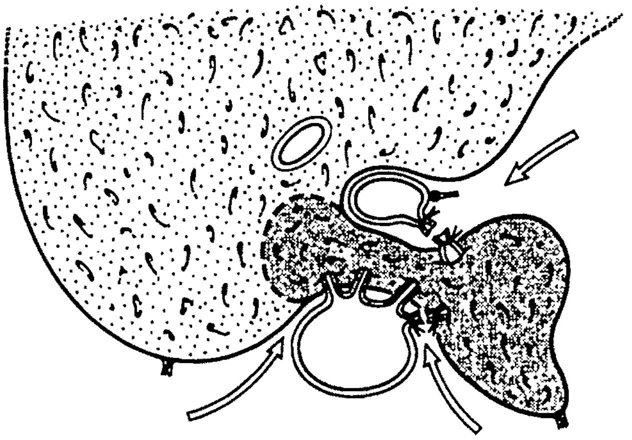

Fig. 4 Lines of approach (arrows) to free the caudate lobe. Compare with *Fig. 1*. Note that the lesser omentum has been opened. The caudate branch of the left portal vein has been tied. The ligamentous attachments of the caudate lobe posteriorly have been opened and dissection of the retrohepatic caudate veins can be approached from the right and/or left side (see text)

3). The left lobe of the liver is mobilized and turned to the right. It is the authors' practice to divide the ligamentous attachments on the left and mobilize the tip of the caudate lobe and its left lateral margin from the IVC before division of the caudate veins (*Figs 3* and *4*). During this dissection it becomes evident whether the caudate lobe is embracing the vena cava posteriorly, in which case no further attempt is made to free the lobe on the left side but an approach should be made from the right[20,21].

After freeing of the ligamentous attachments of the left side of the caudate lobe to the IVC the lobe can be elevated easily. Such hepatic veins as are evident may be encircled and suture-ligated or controlled with clips; in this manner working from the left side of the vena cava towards the right side, extensive and sometimes complete mobilization can be performed (*Figs 3–5*). This technique is most applicable when the caudate lobe is not involved by a bulky tumour, for example in removal of the lobe in continuity to obtain clearance in resection for hilar cholangiocarcinoma. In caudate lobe resection in continuity with left hepatic lobectomy this approach is also valuable, and in extended left hepatic lobectomy it is the authors' practice to attempt to use it as a routine since it gives much less disturbance of the retrohepatic blood flow from the right liver.

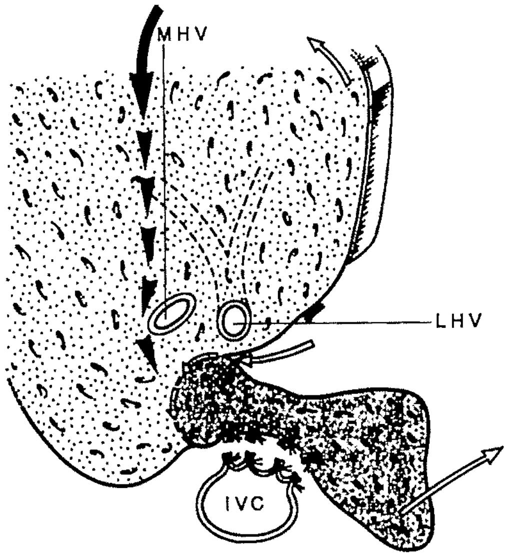

Fig. 5 Parenchymal phase of dissection. Note proximity of the left hepatic vein (LHV) and middle hepatic vein (MHV). The right portion of the caudate lobe lies just to the left of the MHV. The black arrows indicate the line of hepatotomy necessary to approach the caudate lobe from above. The liver is opened just to the right of the MHV along the right margin of segment IV (see text). IVC, inferior vena cava

On the other hand, a bulky tumour within the caudate lobe is often rigid and upward mobilization of the caudate is hazardous. In this case, the retrohepatic veins are best approached from the right side (*Fig. 3*) as previously described[20]. Should right hepatic resection or extended right hepatic resection be contemplated in continuity with the caudate lobe then an approach from the right is easier and is a simple extension of right hepatectomy. The approach to the caudate veins from the right side involves initial complete mobilization of the right hepatic lobe by division of its peritoneal attachments. The right lobe is turned over toward the left and the retrohepatic veins are dissected serially, beginning from below behind the caudate process and extending upward with division of all veins until the major hepatic trunks are reached[7]. As this dissection is carried out it is easy to extend it over the anterior surface of the IVC to the left side until the caudate lobe is completely mobilized and freed from the vena cava[20] (*Fig. 4*).

For right or left hepatic resection involving division of the middle hepatic vein, the caudate lobe is easily removed without danger of tearing the middle hepatic vein since this may be controlled extrahepatically for left-sided resections or intrahepatically for resections on the right side. However, in resection of the caudate lobe as an isolated procedure, and particularly should there be a bulky tumour within the caudate, it is important to recognize the danger that may arise from haemorrhage from the middle hepatic vein should this be torn posteriorly[5]. In this instance the authors have found it valuable to isolate the left and middle hepatic veins by opening up the tunnel between the left hepatic vein and the IVC at the upper end of the caudate lobe (*Fig. 3*) and passing a clamp across the left and middle hepatic veins. This gives temporary control during the parenchymal phase of dissection of the portion of the caudate lobe which lies anterior to the IVC (*Fig. 5*). Some authors have split the liver anteriorly in the Glissonian plane separating the right and left liver and dividing the liver along the right margin of segment IV (*Fig. 6*) so as to approach the caudate lobe in this fashion[5]. A combination of these techniques allows preservation of middle hepatic venous flow and good control of bleeding.

Approaches to caudate lobectomy are thus dependent largely on the size and location of the lesion, the type of associated resection and the presence of scarring from previous resection. In five cases in this series the approach was from the left; this approach was used in two patients because of previous right hepatic lobectomy resulting in extensive scarring. In one patient the approach was performed centrally with an associated central hepatectomy allowing removal of segments IV, V and VIII in continuity with segment I. In practice the liver is frequently rotated from side to side during the resection.

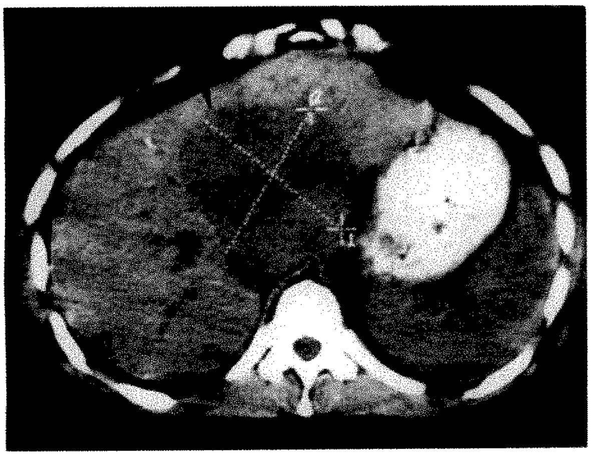

Fig. 6 Computed tomography of the liver in a 25-year-old woman with symptomatic focal nodular hyperplasia in the caudate lobe compressing the inferior vena cava and portal vein without invasion. Freeing of this tumour necessitated an approach to the retrohepatic veins from both the right and left sides

Patients

Twenty-one consecutive patients who underwent caudate lobe (segment I) resection between March 1992 and September 1994 were identified from a prospective database by which all hepatobiliary surgical cases at this hospital are followed. Of 281 liver resections performed during this period, 28 included some form of caudate lobe resection. For the purpose of this review, only 21 patients who had complete caudate lobe resection were included. Four of these 21 underwent isolated complete caudate lobectomy whereas 17 had complete caudate lobe resection in association with some other major hepatectomy.

The 21 patients were nine men and 12 women of median age 55 (range 25–81) years. The most common diagnosis was metastatic colorectal cancer (nine patients). Of the four patients who underwent repeat liver resections, three procedures were for recurrent metastatic colorectal cancer and one for recurrent hepatocellular cancer. Of these four patients, three had a previous right and one a previous left hepatectomy.

This review focuses on the technique of resection, intraoperative events, operating time, blood loss and the ability to obtain negative resection margins. The duration of intensive care monitoring and hospital stay was also noted. The purpose of this review is to report technique and no long term follow-up is intended. However, follow-up at a median of 11 months is reported.

Results

The procedures most commonly performed were extended left hepatic lobectomy with *en bloc* complete caudate lobectomy (four patients) and left hepatectomy with *en bloc* caudate lobectomy (five). Four patients underwent isolated complete caudate lobe resection. Two of these procedures were for recurrent metastatic colorectal cancer, one for recurrent hepatocellular cancer and one for a symptomatic 10-cm caudate mass discovered to be focal nodular hyperplasia (*Fig. 5*).

The median operating time was 5 h (range 3 h to 7 h 20 min). The median blood loss was 1160 (range 300–5000) ml. Seven patients required allogeneic blood transfusion and two received autologous blood. Total vascular occlusion was not used. An intermittent Pringle manoeuvre was used in 11 patients with a median occlusion time of 21 (range 11–35) min. All patients were monitored in the recovery room overnight and then transferred to a surgical ward. Only one patient required intensive care unit monitoring during the hospital stay; he went on to die from liver failure. The median hospital stay was 11 (range 6–51) days.

Complete caudate lobe resection alone or combined with another major resection was possible in all patients. The pathological margins following isolated caudate lobectomy were positive in two instances. One patient had a positive inferior vena caval margin after extensive *en bloc* vena caval resection and one had a positive deep, retroperitoneal soft tissue margin after resection of a 5·2-cm caudate mass. The approach to resection was most commonly from the right side (11 patients), however a left approach was performed in five and a central anterior approach in one. The remaining four procedures were performed using a combined left and right approach. The mean diameter of the caudate lobe lesion was 6·3 cm, ranging from a 2-cm cholangiocarcinoma to a 33-cm hepatocellular carcinoma. No difficulty was encountered as a result of caudate lobe hypertrophy in patients with previous hepatic resection.

There were nine major complications in eight patients (38 per cent morbidity rate), including two deaths (10 per cent mortality rate). One patient died from a massive upper gastrointestinal haemorrhage 21 days after left hepatectomy, *en bloc* caudate lobectomy and portal vein resection. The patient had been recovering slowly from the resection with good liver function. The second patient suffered progressive liver failure, hepatorenal syndrome and encephalopathy, and died 51 days after the procedure. The most common complication overall was a bile collection or biliary fistula, which occurred in three patients. There were two minor wound infections.

After a limited median follow-up of only 11 months, 12 patients are free from disease. One patient is dead from an early liver recurrence from hepatoma, one from recurrent liver metastases from rectal cancer at 12 months and a third from recurrent cholangiocarcinoma at 18 months. Three patients are alive with recurrent disease and one patient is alive after an incomplete, palliative resection of a large symptomatic hepatoma. Of the six patients with recurrent disease, four had recurrence in the liver alone away from the resection margin, one had both liver and lung metastases from rectal cancer, and one had periportal nodal recurrence of cholangiocarcinoma.

Discussion

Resection of the caudate lobe has been used infrequently in the past, partly because of the difficulty of dissection and partly because of a perception of early involvement of the IVC or portal vein by tumour. Precise anatomical knowledge of the caudate segment, improvements in perioperative care and recent descriptions of surgical technique for caudate lobectomy have resulted in more widespread use of this procedure. The caudate lobe can be the origin of primary liver tumours or the sole site of metastases to the liver. More commonly, the caudate lobe is involved by extension from tumours in other liver segments. Although wedge or partial resection of the caudate lobe is often possible, it is less controlled and may be more dangerous than complete caudate lobectomy. Inadequate tumour clearance is also a major concern. The present authors now advocate *en bloc* complete caudate lobectomy for all tumours involving the caudate lobe. Some authors recommend routine caudate lobe resection for all hilar cholangiocarcinomas, given the high incidence of microscopic caudate duct involvement[4].

Previous series and case reports of caudate lobe resection are summarized in *Table 1*. The largest series is a review of hepatic resection for hilar cholangiocarcinoma from Japan reported by Nimura *et al.*[4]. They report 45 complete caudate lobe resections for microscopic involvement of caudate bile ducts, including three isolated caudate lobectomies. The most common operation was extended left hepatectomy with *en bloc* complete caudate lobectomy (15 of 45). Overall 41 per cent of patients suffered a postoperative complication, the most common being wound infection and biliary fistula. The operative mortality rate was 7 per cent. The next largest series is that of Elias *et al.*[24]. They report 20 resections involving the caudate lobe, only seven of which were complete caudate lobectomies. None of these patients received isolated caudate lobe resection. There was no operative death but operative morbidity included four cases of atelectasis, one biliary fistula and one patient with transient hepatic failure[24]. The mean blood loss was 1749 ml and mean operating time 285 min. In the present series there were two deaths (10 per cent), both in patients with associated major lobar resection. Only one patient required admission to the intensive care unit and only seven needed blood transfusion. Overall, the results of previous reports and the present series compare favourably with other series of major hepatic resection[17]. While long term follow-up is not available, long-term survival is expected to be similar to that in other series of liver resection given the similar incidence of tumour-free margins.

Preoperative imaging cannot accurately differentiate tumour invasion from compression of the IVC and of the portal vein, and the majority of caudate lobe masses deserve operative exploration to determine resectability. Complete mobilization of the liver must be undertaken, including rotation of the liver and division of the caudate veins so as to define adequately the extent of tumour involvement. Surprisingly, many tumours thought to invade the vena cava can be dissected free of the cava in a tumour-free plane. In selected cases the IVC can be resected in part or *en bloc* with the caudate lobe [22,23], but this is usually not necessary. Short segments of the IVC can be repaired or reconstructed with autogenous grafts, while longer segments may require a prosthetic graft. A

Table 1 Literature review of caudate lobe resections reported since 1990

Reference	Year	No.	Diagnosis	Procedure	Comments
Takayama *et al.*[11]	1990	1	Hepatoblastoma	Left hepatectomy with complete caudate lobectomy	Neoadjuvant therapy
Lerut *et al.*[20]	1990	1	Benign adenoma	Isolated caudate lobectomy	Technique: right-sided retrohepatic approach to caudate veins
Moriura *et al.*[2]	1990	3	Varied	Combined IVC resection	Technique: IVC reconstruction
Nimura *et al.*[4]	1990	45	Cholangiocarcinoma	Complete *en bloc* caudate lobectomy	Advocate routine complete caudate resection for cholangiocarcinoma
Takayama *et al.*[22]	1991	1	Hepatoblastoma	Extended left hepatectomy with caudate lobectomy and IVC resection	No IVC reconstruction necessary after resection for chronic occlusion
Gardner *et al.*[23]	1992	1	Metastatic colonic cancer	Caudate lobectomy with IVC resection	Technique: use of Gott shunt during IVC resection
Yamamoto *et al.*[5]	1992	1	Hepatoma	Isolated caudate lobectomy	Technique: transhepatic approach
Elias *et al.*[24]	1992	20	Varied	7 complete, 13 partial, 1 isolated caudate lobectomy	Emphasize varied approach to caudate; no deaths
Miyagawa *et al.*[7]	1992	1	Benign adenoma	Isolated caudate lobectomy	Technique: vascular isolation with temporary caval occlusion
Iyomasa *et al.*[8]	1992	1	Cholangiocarcinoma	Isolated caudate lobectomy	Technique: isolated caudate lobectomy
Colonna *et al.*[3]	1993	3	FNH, metastatic colonic cancer	3 isolated caudate lobectomies	Technique: left approach to caudate veins
Shimada *et al.*[1]	1994	9	Hepatocellular carcinoma	2 complete caudate lobectomies; 7 partial caudate lobectomies	High morbidity rate; high rate of early recurrence for hepatocellular cancer
Kosuge *et al.*[9]	1994	1	Hepatoma	Isolated caudate lobectomy	Technique: counterstaining
Yanaga *et al.*[10]	1994	2	Hepatoma	Isolated caudate lobectomy	Technique: vascular isolation by occlusion of hepatic veins
Present series	1996	21	Varied	21 complete caudate lobectomies; 4 isolated caudate lobectomies	—

FNH, focal nodular hyperplasia; IVC, inferior vena cava chronically occluded IVC can be resected without reconstruction as abundant collateral vessels have usually developed[22].

While techniques involving complete vascular isolation can be used for caudate lobe resection, it is of interest that the authors have not had recourse to this in any patient in this series; they have employed their previously published technique[18] involving the maintenance of a low central venous pressure with dissection carried out in a 15° Trendelenburg position to avoid air embolism. Dissection of the hepatic veins is facilitated with this technique.

It has likewise been found unnecessary to employ elaborate techniques of hepatotomy to carry out the majority of caudate lobe resections and been found that, by rotation of the liver from side to side, the peritoneal attachments and all caudate veins along the retrohepatic vena cava are readily approached and ligated. However, for bulky tumours the authors find it essential to temporarily clamp the middle and left hepatic veins during the deep part of the parenchymal transection.

The series reported demonstrates the feasibility and safety of caudate lobe resection according to general principles of liver resection: isolation of segmental inflow and outflow with controlled parenchymal dissection. The addition of caudate lobectomy to major liver resection does not add significantly to the morbidity or mortality of the procedure.

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British Journal of Surgery 1996, 83, 1082–1085

Early measurement of interstitial fibrosis predicts long-term renal function and graft survival in renal transplantation

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This study investigated the relationships between renal allograft interstitial fibrosis, renal function and graft survival. A total of 107 consecutive renal transplant recipients immunosuppressed with cyclosporin were studied. Needle core transplant biopsies were performed before operation and at 1, 6 and 12 months after transplantation. Allograft fibrosis was assessed by histomorphometric analysis of graft interstitial volume fraction. Renal function was measured by isotopic glomerular filtration rate (GFR) measurement at the same time points. Interstitial volume fraction was already high in preperfusion biopsies, significantly increased with time but stabilized at 6 months after transplantation. GFR correlated negatively with interstitial volume fraction at 6 months ($P = 0·05$). Interstitial volume fraction at 1 month was not a useful predictor of subsequent graft survival but for allografts surviving to 6 months an interstitial volume fraction above 25 per cent predicted significantly poorer survival ($P = 0·04$). It provides an objective measure of chronic allograft damage and may prove to be a useful surrogate endpoint in the study of therapeutic intervention.

Although the introduction of cyclosporin has dramatically improved the short-term results of renal transplantation[1,2], the half-life of first cadaveric renal transplants remains at 6–7 years[3–7]. Progressive and irreversible decline in renal function is a well recognized event in renal transplant recipients immunosuppressed with cyclosporin and conventional immunosuppressive drugs[4,5,8–13]. The accompanying histological picture is dominated by marked interstitial fibrosis but the pathophysiology of this condition is not understood and no effective therapy is yet available.

The development of chronic transplant damage usually takes a number of years and effective study of this problem would be enhanced by developing surrogate endpoints for analysis. In this study sequential renal transplant biopsies were performed and analysed by a histomorphometric method to assess the volume fraction of the interstitium. The findings were correlated with renal function and graft survival.

Patients and methods

A total of 130 consecutive patients undergoing cadaveric renal transplantation during the period 1989–1992 were studied. All patients received immunosuppression with cyclosporin either as dual therapy (cyclosporin at an initial dose of 17 mg per kg per day reducing to 7 mg per kg per day by 6 weeks after transplantation plus reducing doses of prednisolone) or as triple therapy (cyclosporin at an initial dose of 10 mg per kg per day reducing to 5 mg per kg per day by 6 weeks after transplantation plus azathioprine 1 mg per kg per day plus reducing doses of prednisolone). Some patients on dual therapy received nifedipine as part of a randomized trial of its effects on cyclosporin nephrotoxicity[14].

Renal function was assessed by glomerular filtration rate (GFR) measurement at 1, 6 and 12 months after transplantation. This was performed using a single-shot isotope technique with ^{51}Cr–ethylenediamine tetra-acetic acid. Needle core transplant biopsies were taken with an 18-G needle mounted in a spring-loaded biopsy gun[15]. A preperfusion needle core biopsy was performed immediately before operation and follow-up biopsies were taken at 1 week, 1 month, 6 months and 12 months after operation. Transplant biopsies were fixed in 10 per cent formalin and paraffin embedded; sections were cut at 2 μm and stained with haematoxylin and eosin.

Graft fibrosis was assessed using a histomorphometric method carried out by a single observer (T.A.M.). An experienced consultant histopathologist examined all material first to exclude biopsies showing acute rejection, as this is known to cause reversible expansion of the interstitium[16,17]. After projecting the microscope slide image on to a wall-mounted matrix, a point counting method was employed to assess the interstitial volume. Twenty-five points from each of eight randomly selected fields were counted for each biopsy. The interstitial volume fraction was calculated as the ratio of the number of points overlying the interstitium to the total number of points counted (200) and was expressed as a percentage. Only cortical areas of the biopsies were analysed and a minimum of three glomeruli was considered necessary to define an adequate biopsy. This method gave a standard error of the mean of less than 10 per cent and the intraobserver error was also less than 10 per cent.

Statistical analysis

Values are quoted as mean(s.e.m.). Normal distribution was confirmed using the Kolmogorov–Smirnov test and groups were then compared with a two-tailed Student's t test. Differences were considered significant when $P < 0·05$. Correlation coefficients were used to describe the relationships between graft fibrosis and renal function. Kaplan–Meier graft survival curves were constructed and differences compared with the log rank statistic.

Results

The mean(s.e.m.) preperfusion interstitial volume fraction was 19·6(1·22) per cent compared with approximately 5 per cent for normal human kidneys. Interstitial volume fraction increased significantly at 1 and 6 months after transplantation but then stabilized, and there was no further rise by 12 months (*Fig. 1*). GFR correlated negatively with interstitial volume fraction at 6 months after transplantation ($P < 0·05$; *Fig. 2*) and there was a

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Paper accepted 21 November 1995

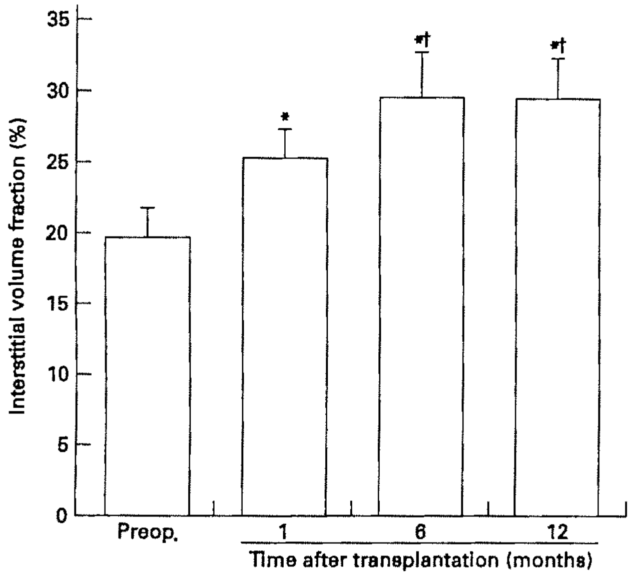

Fig. 1 Changes in renal transplant interstitial volume fraction with time. Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* preoperative value; $‡P < 0{\cdot}05$ *versus* 1 month after transplantation (*t* test)

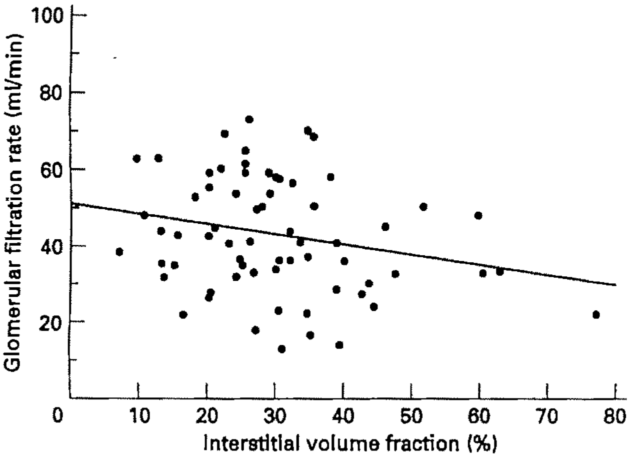

Fig. 2 Renal allograft glomerular filtration rate (GFR) and interstitial volume fraction 6 months after transplantation. GFR correlated negatively with interstitial volume fraction ($P < 0{\cdot}05$, Pearson correlation coefficient)

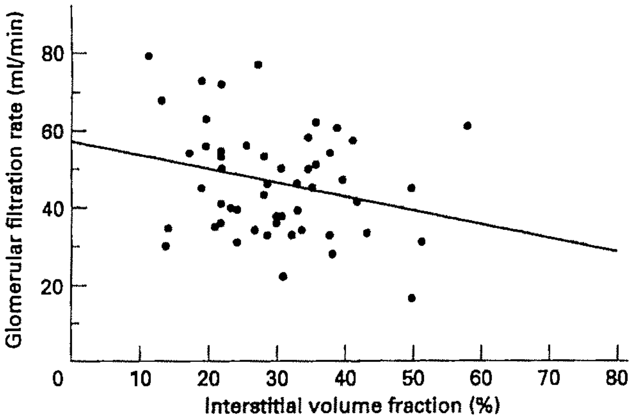

Fig. 3 Renal allograft glomerular filtration rate and interstitial volume fraction 12 months after transplantation. There was no significant correlation ($P = 0{\cdot}07$, Pearson correlation coefficient)

similar relationship at 12 months which was not significa ($P = 0{\cdot}07$; *Fig. 3*). Mean(s.e.m.) interstitial volume fractic was marginally lower in patients receiving cyclospor 17 mg per kg per day with nifedipine (27·2(2·4) per cen than in those having cyclosporin 17 mg per kg per d without nifedipine (35·4(3·8) per cent, $P = 0{\cdot}06$). The were no statistical differences between interstitial volun fraction measured in patients receiving high-do cyclosporin (30·3(2·9) per cent) and in those having trip therapy including cyclosporin 10 mg per kg per d (29·2(2·4) per cent).

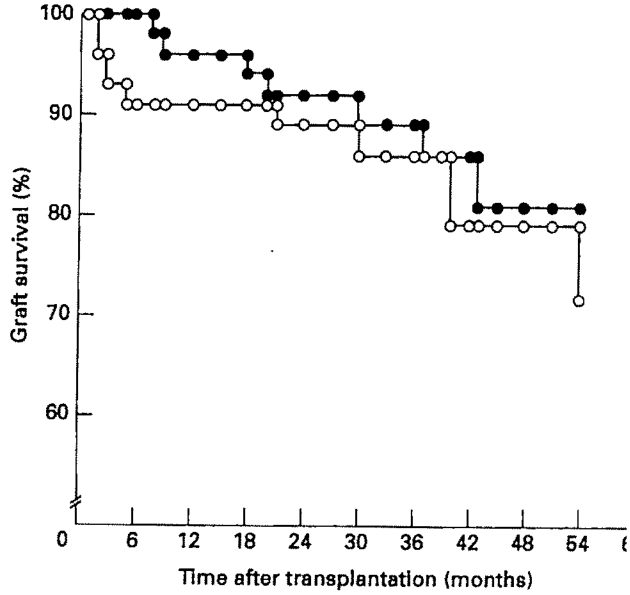

Fig. 4 Graft survival in patients with an interstitial volume fraction above (○) or below (●) 25 per cent 1 month after transplantation

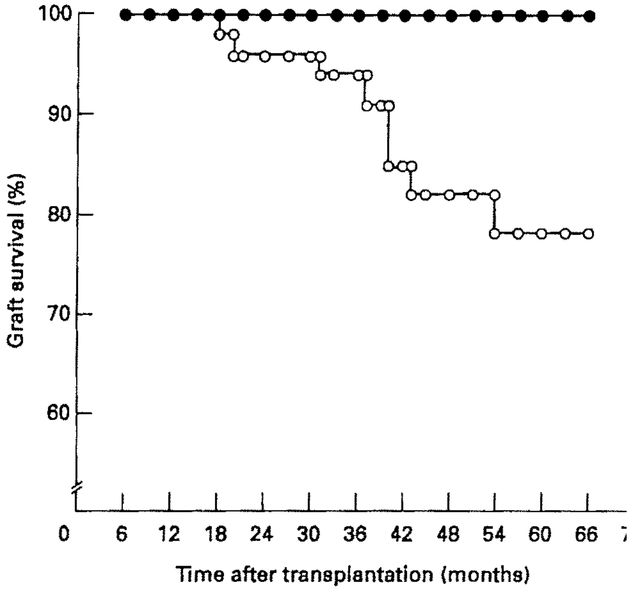

Fig. 5 Graft survival in patients with an interstitial volume fraction above (○; $n = 47$) or below (●; $n = 24$) 25 per cent 6 months after transplantation. Interstitial volume fraction above 25 per cent predicted significantly reduced graft survival ($P = 0{\cdot}04$, log rank test)

The 25 per cent interstitial volume fraction was taken as an arbitrary watershed; this divided patients into two approximately equal groups at 1 month. At this stage there was no significant difference in subsequent graft survival in patients with an interstitial volume fraction of 25 per cent or less and those with a volume fraction above 25 per cent (*Fig. 4*). In renal allografts surviving 6 months after transplantation, in which the interstitial volume fraction was less than or equal to 25 per cent, the subsequent graft survival rate was 100 per cent. In contrast, an interstitial volume fraction of greater than 25 per cent at 6 months predicted significantly reduced subsequent graft survival ($P = 0{\cdot}04$; *Fig. 5*). The median (range) follow-up for all patients was 35 (2–58) months.

Discussion

Modern immunosuppressive regimens based around cyclosporin have dramatically reduced the incidence and severity of acute rejection episodes and have been responsible for improved graft survival. None the less, in the longer term it is common for renal allografts to demonstrate a progressive and irreversible decline in renal function leading to eventual failure[4,5,8–13]. The histopathological picture associated with chronically failing renal transplants is dominated by interstitial fibrosis, tubular atrophy and glomerulosclerosis[3,8–21]. Interstitial fibrosis is perhaps the most prominent and consistent feature and represents a final common pathway in the response of the kidney to any injury, be it mediated by immunological or ischaemic mechanisms[22]. Although this process is usually ascribed to chronic rejection, the issue is confused and there is certainly an overlap with the syndrome of chronic cyclosporin toxicity[23], which has been shown to have a role in the development of interstitial fibrosis[24–26]. It is also clear that acute and chronic allograft rejection and cyclosporin-related nephrotoxicity can occur at the same time in the same patient[26–30]. Previous studies have shown increased interstitial volume fraction in patients with renal transplants treated with cyclosporin compared with those who were not[16] and an increase in interstitial volume fraction with high- *versus* low-dose cyclosporin[17,32]. Renal interstitial fibrosis has been demonstrated in heart transplant recipients immunosuppressed with cyclosporin[33,34] and in patients receiving cyclosporin for other reasons[32,34–37]. Furthermore, cyclosporin has been shown to increase levels of collagen type I and IV messenger RNA within the renal interstitium[38].

The histomorphometric analysis described in the present study does not measure interstitial fibrosis specifically but has been used as an indicator of this parameter. In view of this it was considered important to exclude biopsies showing the changes of acute rejection as the associated oedema is known to increase the relative size of the interstitium[16,17]. The other features of chronic allograft damage such as tubular atrophy, glomerulosclerosis and vascular obliteration have not been addressed in this study.

The results presented show that measurement of interstitial volume fraction can be used as a predictor of subsequent graft survival in allografts biopsied at the 6-month time point. Interstitial volume fraction may therefore prove to be a useful surrogate endpoint in studies of therapeutic modalities that may prevent chronic allograft damage. The limitation of graft survival as an endpoint is that it takes many years to assess differences between groups being compared but, as interstitial volume fraction measurement is an interim endpoint, it does not suffer from this problem. Early recognition of increasing interstitial volume might also be useful in predicting which grafts may benefit from a reduction in cyclosporin dosage or even its complete withdrawal and conversion to conventional immunosuppression. A surrogate endpoint is useful only if it defines grafts at risk of progressively declining function and eventual failure early enough to allow intervention. The timing of biopsies is clearly very important and this study has demonstrated that 1 month after transplantation is too soon to make predictions about subsequent outcome. The maximum increase in interstitial volume fraction appears to be reached 6 months after translantation; this finding is in agreement with that of Ruiz *et al.*[16], who found an increased interstitial volume fraction associated with cyclosporin therapy but noted that the increase was only apparent by 6 months or more. This raises the question of what happens between 1 and 6 months after transplantation as it is likely that the sooner the predictive changes in interstitial volume fraction are picked up, the more likely it is that effective treatment can be given. It is suggested, therefore, that future studies should include a biopsy at the 3-month time point.

The method of assessing interstitial volume fraction described here has a number of limitations. In particular, the point counting involved is time consuming and labour intensive. If the method is to be used more widely it will need to be modified to include a staining procedure to demonstrate the interstitium and the incorporation of an image analysis system to provide rapid automated results.

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British Journal of Surgery 1996, 83, 1086

Surgical workshop

Intra-abdominal Sengstaken–Blakemore tube placement for acute venous outflow obstruction in reduced-size liver transplantation

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Reduced-size liver transplantation using *ex vivo* graft reduction or splitting has become the standard procedure in children with biliary atresia[1–3]. In up to 10 per cent of patients biliary atresia is associated with a polysplenia syndrome which includes absence of inferior vena cava, preduodenal portal vein, multiple spleens, intestinal malrotation and situs inversus[3]. Reduced-size liver transplantation in combination with this unusual situation carries an increased risk of venous outflow obstruction, mainly because of piggyback implantation[4].

This report is of the successful management of acute venous obstruction after transplantation of a right liver lobe by the placement of a Sengstaken–Blakemore tube within the hepatic fossa.

Surgical technique

A 15-year-old girl with biliary atresia associated with polysplenia syndrome received the right lobe from a split liver. The donor:recipient body-weight ratio was 1·63 (80:49 kg). Her inferior vena cava was absent. The right hepatic vein joined the right atrium directly, and was divided. The upper cuff of the vena cava of the graft was therefore anastomosed end to end to the common collector of the middle and left hepatic veins of the recipient. The position of the right lobe graft in its fossa led to kinking of the upper caval anastomosis. Major bleeding from the transected surface and liver congestion were eventually abolished by a slight clockwise rotation of the graft. A Sengstaken–Blakemore tube was therefore inserted into the right subphrenic space. The 'gastric' and 'oesophageal' balloons were inflated to maintain the graft in midline position (*Fig. 1*).

After operation Doppler ultrasonography was repeated daily to ensure that venous outflow was maintained. On day 7 the balloons were deflated under Doppler ultrasonographic guidance. The Sengstaken–Blakemore tube with balloons deflated was left in place for 48 h and, after a final satisfactory Doppler ultrasonographic scan, it was removed using slight traction without need for reoperation.

Discussion

Acute hepatic vein obstruction has been observed after right hepatectomy[5] or transplantation of reduced-size liver[4] as a result of kinking of the left hepatic vein following prolapse of the liver into the right subphrenic space. In reduced-size liver transplantation the risk of venous outflow obstruction is increased by direct implantation of the left hepatic vein (left or left lateral lobe) into the recipient vena cava using the piggyback technique. When the graft is not fixed alongside the vena cava axis, it is free to swing to the right. In the present case of a right lobe graft, the absence of vena cava and the location of the upper caval anastomosis, toward the left, were the anatomical reasons for acute venous obstruction. Satisfactory venous drainage was restored when the graft was stabilized in a midline position. This was achieved by the placement of a Sengstaken–Blakemore tube behind the liver. The advantages of the Sengstaken–Blakemore tube over a Silastic (Dow Corning, Reading, UK) tissue expander[3] are the possibility to deflate or reinflate each balloon separately with Doppler ultrasonographic monitoring, and to remove the tube without reoperation after the liver has become fixed in a haemodynamically correct position.

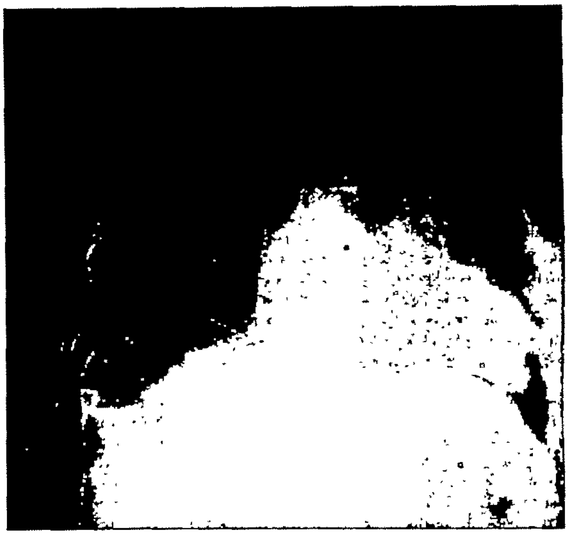

Fig. 1 Abdominal radiograph showing the Sengstaken–Blakemore tube with inflated balloons placed in the right subphrenic space

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Paper accepted 1 November 1995

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British Journal of Surgery 1996, 83, 1087–1090

Wound metastases following laparoscopic and open surgery for abdominal cancer in a rat model

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The recent application of laparoscopic resection techniques to malignant disease has raised safety concerns due to metastasis to surgical access wounds. The significance and incidence of this problem are controversial. In the present study a rat model, in which an implanted tumour was lacerated, was used to investigate whether application of laparoscopic techniques for malignant abdominal disease leads to an increased risk of tumour dissemination and implantation within the peritoneal cavity, and abdominal wall wounds. Malignant cells were implanted into the abdominal wall of 42 rats, resulting 7 days later in the growth of a tumour measuring 20–25 mm in diameter. There were three control groups: no surgery ($n = 6$); blunt manipulation of the tumour laparoscopically ($n = 6$); and blunt manipulation of the tumour at laparotomy ($n = 6$). Twenty-four rats underwent surgical laceration of the tumour capsule at either laparoscopy ($n = 12$) or laparotomy ($n = 12$). All rats were killed 1 week later, and examined for macroscopic evidence of tumour metastasis. The abdominal surgical wounds were excised for independent microscopic examination by a histopathologist. Growth of the primary tumour was greater in rats that had an operation than in unoperated controls, and was greatest after laparotomy. However, wound metastases were five times more likely after laparoscopic tumour laceration than after the same procedure through an open incision (ten of 12 rats *versus* two of 12, $P = 0{\cdot}0033$). Wound metastases following laparoscopic tumour manipulation are an important and real problem, with significant implications for the application of laparoscopic techniques to excise malignant disease in humans.

Since the introduction of laparoscopic cholecystectomy, there has been a rapid expansion in the application of laparoscopic techniques to other areas of abdominal and thoracic surgery, including the resection of malignant disease. Descriptions of laparoscopic colectomy for colonic carcinoma, gastrectomy for gastric carcinoma, pancreatectomy, nephrectomy and liver resection have been either published[1–3] or reported at surgical meetings. Laparoscopic colonic resection in particular is now being applied widely in many centres.

Recently, however, several case reports have appeared in the surgical literature describing metastases in the wounds created for the introduction of laparoscopic instruments into the abdominal or thoracic cavity, following tumour resection. While this has been reported especially after laparoscopic resection of colonic and gallbladder carcinoma[4–6], wound metastasis following laparoscopy for pancreatic carcinoma, during which the primary tumour was not manipulated, has also been reported by several authors[7–9]. As a consequence, many surgeons have expressed concern about the applicability of laparoscopic techniques to the surgical treatment of malignancy. While laparoscopy often reduces the short-term morbidity of surgery by reducing wound-related pain[10], and speeds postoperative recovery[11], enabling patients to return to work earlier[12], all of these short-term benefits are irrelevant if the technique increases the risk of tumour recurrence.

The best way to determine the risk and significance of wound metastases is by conducting a prospective randomized trial of laparoscopic *versus* conventional surgery in patients undergoing surgery for malignancy. However, this may require large numbers to achieve significance, and results are unlikely to be forthcoming for many years.

Previous experience using a tumour cell line in rats has shown that a malignant tumour can be reliably implanted in laboratory rats by the injection of a cell suspension, to create a model which allows the investigation of the effect of laparoscopy on intra-abdominal malignancy and tumour implantation[13,14]. The aim of this study was to determine whether the application of laparoscopic techniques to the treatment of malignant abdominal disease in this rat model leads to an increased risk of tumour dissemination and implantation within the peritoneal cavity, and abdominal wall wounds.

Materials and methods

Forty-two male Dark Agouti rats weighing 240–280 g (median 250 g) were injected in the left flank abdominal musculature with a suspension of mammary adenocarcinoma tumour cells (2×10^8 in a volume of 200 μl). Cells had previously been prepared by homogenizing tumours resected from carrier rats. Preliminary work with this model confirmed that after 7 days the tumour would grow reliably to form a mass approximately 20–25 mm in diameter, and comprising approximately 1–2 per cent of the rat's body weight. Tumours implanted in the lateral abdominal wall were still covered by a thin layer of peritoneum at this stage, and were readily visible at either laparoscopic or open surgery.

Seven days after tumour implantation rats in the following groups underwent an operative procedure: anaesthesia only in the controls (group 1, $n = 6$); no tumour manipulation at either laparoscopy ($n = 6$) or laparotomy ($n = 6$) (group 2); tumour laceration at either laparoscopy ($n = 12$ rats) or laparotomy ($n = 12$) (group 3). All rats were anaesthetized during these procedures with a combination of halothane and nitrous oxide supplemented by oxygen via a close-fitting mask. The respiratory status of animals was closely monitored throughout anaesthesia, and all surgical procedures were performed under sterile operating conditions.

Paper accepted 14 March 1996

Rats in the control group were anaesthetized for a 30-min period, but underwent no operative procedure. Laparotomy was performed through a 3-cm midline incision to expose the abdominal cavity and its contents. Tumour was visible bulging into the abdominal cavity but it was covered by peritoneum. In the groups who underwent tumour laceration, the tumour capsule was lacerated once through the covering peritoneum using the tip of an 18-gauge needle. The abdomen was subsequently closed with 3/0 polypropylene sutures in two layers.

For laparoscopy, pneumoperitoneum was achieved using a conventional Veress needle placed through an umbilical stab wound. A disposable minilaparoscopy cannula (Imagyn Medical, Laguna Niguel, California, USA) was then slid over the needle to provide access for a 2-mm minilaparoscope (Imagyn Medical) which enabled continuous insufflation of gas. Carbon dioxide was insufflated at a rate of 0·1 l/min and a pressure of 2 mmHg. The previously implanted tumour was easily seen to be bulging into the abdominal cavity when viewed through the laparoscope. An 18-gauge intravenous cannula was introduced through the abdominal wall opposite the tumour, providing access for subsequent instrumentation. In the group undergoing laceration, a long needle was introduced through this cannula to create a single tumour laceration under direct vision. The cannula was left *in situ* as a laparoscopic 'cannula' after tumour laceration and was used to vent insufflated gas. Pneumoperitoneum was maintained for 60 min with a constant gas flow through the venting cannula. The non-laceration laparoscopy group underwent the same manoeuvres, with the exception of tumour laceration. Care was taken to ensure that the respiratory status of the animal was not compromised. After 60 min the insufflating and venting cannulas were removed, and the puncture sites were closed with interrupted 3/0 Prolene (Ethicon, Edinburgh, UK) sutures. All operations were performed by the same investigator.

Seven days after the operative procedure, the animals were killed, the abdominal cavity was opened, and the dimensions of the primary tumour were measured. Both the laparotomy and laparoscopy access wounds were examined directly for evidence of macroscopic tumour metastasis before the wounds were excised for histopathological examination. Any other areas suspicious of tumour involvement or metastasis were also excised for histological analysis. Excised specimens were fixed in buffered formalin before embedding in paraffin for sectioning and subsequent staining with haematoxylin and eosin. All specimens were examined by a histopathologist who was unaware of which group the animal came from, and who was also unaware of the site of origin of the histological specimens. The weights of animals in each group were similar before operation, and were not significantly altered by either tumour laceration or the surgical access technique.

Statistical analysis of data sets was performed using either the Mann–Whitney U test or the Fisher's exact test. The protocol for this study was approved by the Animal Ethics Committees of the Institute of Medical and Veterinary Science and the University of Adelaide.

Results

Primary tumour growth

Primary implanted tumours in all groups (control, laparotomy and laparoscopy) enlarged in the week following general anaesthesia and associated surgery (*Table 1*). The size of the primary tumour at the end of the study was similar in all groups ($P = 0{\cdot}96$). The implanted tumours at the time of laparotomy were approximately 25 per cent smaller in maximum dimension than those measured in either the control ($P = 0{\cdot}01$) or laparoscopy groups ($P = 0{\cdot}05$). Enlargement of the primary tumour after laparotomy was greater than after laparoscopy ($P = 0{\cdot}04$), or anaesthesia (control group) ($P = 0{\cdot}09$). Tumour size and growth were not related to body weight.

Table 1 Tumour dimensions

	Maximum dimension (mm)		
	Control ($n = 6$)	Laparoscopy ($n = 18$)	Laparotomy ($n = 18$)
Preoperative	33 (25–40)	30 (15–40)	23 (15–35)
7 days after operation	55 (45–70)	55 (40–70)	53 (30–70)
Percentage increase	78 (43–200)	93 (50–225)	133 (50–225)

Values are median (range)

Table 2 Wound metastases 1 week after tumour laceration

	Laparoscopy ($n = 12$)	Laparotomy ($n = 12$)	P*
Macroscopic metastases	5	1	0·15
Microscopic metastases	10	2	0·0033

*Fisher's exact test

Table 3 Location of wound metastases following laparoscopic tumour laceration

	No. of metastases
No tumour in either wound	2
Wound for laparoscope only	4
Wound for manipulating/lacerating instrument only	4
Both wounds	2

Wound metastasis

No macroscopic or microscopic tumour metastases developed in the wounds of rats that had either laparoscopy or laparotomy without tumour laceration. Tumour metastases were present in the wounds of rats that had tumour laceration by either a laparoscopic or open surgical technique (*Table 2*). Metastases were significantly more common in the group having laparoscopy ($P = 0{\cdot}0033$). The distribution of tumour metastases in the port wounds is summarized in *Table 3*.

Tumour metastasis within the peritoneal cavity

No tumour dissemination or peritoneal invasion was evident in the control, laparotomy or laparoscopy groups of rats that did not undergo tumour laceration. In the two groups having tumour laceration there was no macroscopic evidence of tumour dissemination beyond the immediate site of tumour laceration in either group of rats. At the site of tumour laceration, tumour was seen to be growing through the peritoneal covering in all rats.

Discussion

There is controversy about whether the incidence of wound metastases is increased following laparoscopic tumour surgery. This problem may be more likely to occur after laparoscopic surgery because of the promotion of spread, implantation and metastatic growth which could preclude laparoscopic resection of malignant disease[5,6]. However, it is also possible that tumour metastasis may be less likely following laparoscopic surgery as postoperative immune function appears to be less disturbed by the laparoscopic approach[15]. Reports of wound metastases could be anecdotal, and may not reflect the true outcome of laparoscopic resection, which may be advantageous to patients undergoing tumour excision. Metastases may also reflect the tumour stage at the time of laparoscopic excision, and may not be related to any deleterious effect on patient survival.

The recent surgical literature contains an increasing number of reports of wound metastases following laparoscopic procedures for intra-abdominal malignancy[3–9]. A review by Nduka *et al.*[5] has highlighted some case reports describing this complication following laparoscopic resection of colonic and gallbladder carcinoma. This problem is not new, as the gynaecological literature also describes wound metastases following laparoscopy for ovarian carcinoma[16]. It may also occur following laparoscopy in the presence of pancreatic carcinoma, even in the absence of tumour dissection or manipulation[7–9].

Unfortunately, while anecdotal reports may provide evidence of patients who develop laparoscopic wound metastases, the overall incidence cannot be calculated without knowledge of the appropriate denominator, namely, the number of patients who undergo such laparoscopic procedures. Without this, the real importance of these metastases is difficult to assess. The incidence of wound metastases following open surgery for malignancy is also difficult to determine. In a large experience with conventional colectomy for colorectal carcinoma, Hughes *et al.*[17] described 1 per cent incidence of metastases to the surgical access wound. Most patients in this series with incision site recurrences had advanced disease at the time of initial surgery.

While the life expectancy of patients who undergo laparoscopic surgery for advanced malignancy may not be shortened by subsequent port-site metastases, it is disturbing that some wound metastases have occurred in patients who had resection of early-stage carcinomas[18,19]. Tumour recurrence has also occurred in port wounds through which no tumour or specimen was extracted and which had no direct contact with the resected tumour[7–9,16]. It is possible that there is some factor inherent in the laparoscopic techniques or environment which is predisposing to wound metastases. Several other aetiological theories have been proposed[4,5]. The gas flows generated during the pneumoperitoneum may spread tumour cells. Gas leaking around laparoscopic ports may lead to lodging of tumour cells in wounds. Finally, tumour cells may grow more readily in areas of high cell proliferation in healing port wounds. No studies have been published that substantiate any of these claims.

The present study describes a very high rate of wound metastases in rats that underwent laparoscopic tumour laceration compared with the rate in rats that had an identical procedure at open surgery. The presence of tumour in port wounds used for passage of the laparoscope, as well as that used for tumour laceration, suggests that direct implantation of tumour from a tumour-laden instrument or during specimen extraction does not account for all wound metastases. It is likely that free cells lodge in laparoscopic wounds, implant and proliferate, as a result of some factor inherent in the laparoscopic procedure or environment.

Others have demonstrated reduced primary tumour growth after laparoscopy in animal models and have postulated beneficial immunological effects of laparoscopic surgery compared with those of open surgery[20,21]. The differential growth of the primary tumours in this study supports the observations of tumour growth studies. However, the increased incidence of wound metastases suggests that this benefit may be of no practical significance in patients operated on laparoscopically for malignant disease, in whom malignant tissue is breached. While in this study no metastases developed in animals in which the tumour was not lacerated, surgeons should not assume that laparoscopic tumour surgery is safe if no macroscopic breach of the tumour capsule occurs during clinical surgery. The technical difficulties of laparoscopic dissection may make inadvertent tumour laceration more likely than during open surgery, with potentially more serious consequences for patients.

The results of this study add weight to the argument that wound metastasis following laparoscopic manipulation of malignant tumours is an important clinical problem, which must be addressed urgently. The model used offers a unique opportunity to investigate this issue further, and to manipulate the laparoscopic environment in ways that may reduce or eliminate the likelihood of wound metastases. Until a clearer picture emerges, the authors support the contention that laparoscopic surgery for malignant disease should be practised only within well conducted prospective randomized clinical trials.

Acknowledgements

The authors are grateful for the assistance of Mr Robert Locke and M. R. Surgical, Australia who provided the minilaparoscope and access cannulas used in this study. T.E. was supported by a grant from the Anti-Cancer Foundation of the Universities of South Australia, and G.M. by a grant from the Burnside War Memorial Hospital, Burnside, South Australia.

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British Journal of Surgery 1996, **83**, 1090

Surgical workshop

Laparoscopic feeding jejunostomy

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Following the introduction of percutaneous endoscopic gastrostomy (PEG) feeding tubes[1], fewer patients now require formal jejunostomy. It may be impossible or unwise to pass a PEG tube in patients with head and neck cancer because of pharyngeal stenosis or the possibility of later gastric pull-up surgery. These patients frequently require nutritional support, and this can now be provided using a laparoscopic technique for placing a jejunal feeding tube.

Surgical technique

After standard peritoneal insufflation with carbon dioxide, a 10- or 11-mm cannula is introduced subumbilically for the laparoscope. A further 10-mm cannula is placed in the left upper quadrant and a 5-mm cannula, if necessary, in the right upper quadrant. Atraumatic tissue forceps is used to identify the duodenojejunal flexure and the jejunum is 'walked down' for 10–15 cm. At this point the jejunum is held with endoscopic tissue forceps placed through the left upper quadrant cannula. Carbon dioxide is then released from the abdominal cavity, and both the tissue forceps and left upper quadrant cannula are withdrawn simultaneously. The endoscopic forceps holds the jejunum on to the surface of the abdominal wall and a purse string is inserted into the jejunum and a small enterotomy is fashioned. A 14-gauge Foley Silastic (Dow Corning, Reading, UK) catheter is inserted, the catheter balloon is inflated with saline and the purse string is ligated around the catheter. The long end of the purse string with attached needle is used to suture the jejunum to the abdominal wall musculature at the site of cannula insertion. The Foley catheter is sewn to the skin with a retaining suture. Enteral nutrition can be commenced forthwith.

This technique has been employed in a 48-year-old woman with postcricoid carcinoma during radiation treatment. She was maintained successfully on home enteral nutrition for 94 days during her treatment until re-establishment of oral nutrition.

Discussion

Although rarely needed, this technique is simple and quick to perform. It does not require stay sutures or anchors[2,3], or expensive stapling techniques as described by Arnaud *et al.*[4]. Formal laparotomy is not required. It should be possible to use this method to insert tunnelled jejunostomy feeding tubes.

Paper accepted 19 October 1995

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British Journal of Surgery 1996, 83, 1091–1094

Prospective study of the aetiology of infusion phlebitis and line failure during peripheral parenteral nutrition

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Four techniques of administering peripheral parenteral nutrition (PPN) were examined prospectively to investigate the role of mechanical trauma in the development of infusion phlebitis. Patients in group 1 ($n = 15$) were fed via a standard 18-G Teflon cannula which was removed on completion of the infusion and was rotated to the contralateral arm every day. Group 2 patients ($n = 15$) had a similar catheter sited in each forearm simultaneously, with rotation of the side of infusion each day. Patients in group 3 ($n = 17$) had a 15-cm Silastic rubber catheter inserted into a forearm vein and a standard cannula sited in the contralateral forearm, with alternation of infusion each day. Those in group 4 ($n = 13$) had a fine-bore 23-G silicone catheter sited in one arm only. Patients in groups 1, 2 and 3 were fed over 12-h cycles and those in group 4 for a 24-h continuous cycle. A total of 408 patient-days of PPN were given. Mean duration of PPN in groups 1–4 was 7·5, 9, 5·5 and 5 days respectively. Infusion phlebitis was not recorded in patients who had a daily change of cannula (group 1), but occurred in four patients in group 2, eight in group 3 and eight in group 4. Phlebitis scores were 0, 9, 15 and 12 for groups 1–4 respectively. Severe phlebitis and line occlusion occurred more frequently in patients with a 15-cm catheter (group 3) and in those fed continuously over 24 h (group 4). These results suggest that mechanical trauma is an important factor in the aetiology of infusion phlebitis. This can be minimized by reducing the time for which the vein wall is exposed to nutrient infusion and by reducing the amount of prosthetic material within the vein.

Although the use of peripheral parenteral nutrition (PPN) is increasing in the UK, most parenteral nutrition is still administered through a central venous line. One obstacle to the more widespread adoption of PPN is the concern that it is applicable only for limited periods, principally because of the development of infusion phlebitis[1]. The many causes of infusion phlebitis and the many different techniques described to reduce its incidence have been extensively reviewed[2,3]. The authors' own studies suggest that infusion phlebitis can be minimized by intermittent infusion of nutrients and by rotation of venous access sites[4]. Others[5,6] have recently advocated use of long-line fine-bore infant feeding tubes. However, controversy persists as to the optimal means of administering PPN[7–9].

The aim of this study was to compare cyclical rotation of venous access sites and fine-bore feeding tubes with particular attention to the importance of mechanical trauma in the development of infusion phlebitis.

Patients and methods

All patients who required total parenteral nutrition (TPN) over an 18-month period were eligible for the study. Patients were excluded if they already had an indwelling central venous line or if, after initial assessment, they were found not to have suitable forearm veins. No patient was able to take an adequate supply of nutrients by the enteral route. Peripheral cannulas were inserted by a specialist nutrition nurse according to a strict aseptic protocol. No restrictions were placed on the nurse in the siting of the cannula, except that cubital fossa veins were not used. Cannulas were used exclusively for nutritional support; patients who required intravenous antibiotics, other drugs or supplemental fluids had additional venous access. An identical commercially prepared peripheral feeding regimen was used for all patients (P3; Pharmacia, Milton Keynes, UK) to provide 30 kcal per kg per day of non-protein energy and 0·15 gN per kg per day. Trace elements, electrolytes and vitamins were added in the pharmacy according to individual patient requirements.

This study was a prospective randomized trial comparing four groups of patients. Approval to conduct it was granted by the local hospital ethical committee.

In group 1, patients received PPN through a suitable forearm vein with a standard 18-G Teflon cannula (Venflon; Ohmeda, Swindon, UK). The total daily requirement of parenteral nutrition was infused over a 12-h period, almost always at night. After infusion the cannula was removed and the patient allowed to move freely. PPN was restarted 12 h later through a forearm vein in the contralateral arm. Venous access sites on the same forearm vein were often used repeatedly on separate days but this was not a prerequisite of the protocol.

In group 2, patients had a standard 18-G cannula inserted into a peripheral vein in both forearms on entry into the study. PPN was again infused over a 12-h period, following which the cannula was heparin-locked and left *in situ*. PPN was continued through the cannula in the contralateral arm on alternate days, thus allowing a rest period of 36 h before each line was reused. Cannulas were removed only if they became occluded or if there was evidence of phlebitis.

In group 3, patients had a standard 18-G cannula sited in one forearm as used in groups 1 and 2 and, in addition, an 18-G 15-cm polyethylene rubber catheter (Leadercath; Vygon, Cirencester, UK) was sited simultaneously in a contralateral forearm vein. A Seldinger technique was used to insert the longer cannula. PPN was again infused over a 12-h period through alternating forearm cannulas every other day. The cannulas were changed as necessary on occlusion or on the development of phlebitis, always by placing the same type of cannula.

In group 4, PPN was delivered through a fine-bore 23-G 15-cm silicone peripheral feeding line (Epicutaneo Cava Catheter; Vygon, Aachen, Germany) inserted into a suitable forearm vein. Patients received parenteral nutrition as a continuous 24-h infusion with the aid of a volumetric infusion pump. These cannulas were also changed if they became occluded or if the patient developed signs of phlebitis. Patients in group 4 received an identical feed to those in groups 1–3, but the rate of infusion was halved.

The daily care of infusion sites, infusion bag changes and the monitoring of each patient's fluid and electrolyte balance was

Paper accepted 20 November 1995

supervised by a specialist nutrition nurse. All complications and the reason for the changing of lines or venous access sites were recorded. Because grading of phlebitis is imprecise and prone to observer error, it was decided to classify phlebitis as either mild or severe. Mild phlebitis was scored arbitrarily as 1 and was recorded when patients complained of pain over the cannulated vein. Severe phlebitis was scored as 3 and was recorded if there was induration, tenderness or erythema over the cannulated vein. All lines were changed on the first appearance of phlebitis or occlusion. Pharmaceutical methods of reducing phlebitis, such as heparin, hydrocortisone and the use of glyceryl trinitrate, were not used.

Statistical analysis

Data were analysed by the χ^2 test and analysis of variance.

Results

Over the 18-month duration of this study, 78 patients were referred for parenteral nutrition. PPN was not possible in eight patients because of poor peripheral veins. In a further ten patients parenteral nutrition was administered through a pre-existing central line. The remaining 60 patients were randomized; their ages and clinical details are shown in *Table 1*. The four groups were well matched for age and indication for nutritional support, although no patient in group 4 was treated for enterocutaneous fistula. A total of 408 patient-days of PPN were given; 14 patients required conversion to other methods of nutritional delivery (*Table 2*). Data relating to cannula survival and complications are shown in *Table 3*.

Table 1 Patient details

	Group 1	Group 2	Group 3	Group 4
No. of patients	15	15	17	13
Sex ratio (M:F)	8:7	4:11	6:11	5:8
Median (range) age (years)	56 (45–78)	64 (33–84)	62 (37–82)	52 (19–77)
Preoperative PPN				
Inflammatory bowel disease	3	5	4	3
Acute pancreatitis	2	2	2	2
Postoperative PPN				
Failed enteral support	7	6	9	8
Enterocutaneous fistula	3	2	2	0

PPN, peripheral parenteral nutrition

Table 2 Outcome of parenteral nutrition

	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 17$)	Group 4 ($n = 13$)
Total duration of PPN (patient-days)	116	135	92	65*
Mean duration of PPN (days)	7·5	9	5·5	5†
No. of venepunctures	116	64	50	24
Conversion to CPN	3	0	4	1
Conversion to another method of PPN	0	0	0	3
PPN abandoned	0	0	0	3
Total duration of TPN (days)	184	135	157	92†

PPN, peripheral parenteral nutrition; CPN, central parenteral nutrition; TPN, total parenteral nutrition. *$P < 0{\cdot}01$ (group 4 *versus* group 2), $P < 0{\cdot}05$ (group 4 *versus* group 1); †$P < 0{\cdot}05$ (group 4 *versus* groups 1 and 2)

PPN in three patients in group 1 was converted to central feeding after 2, 5 and 14 days because of failure to re-establish venous access. In group 2, all 15 patients completed their TPN requirement using this technique. Five episodes of phlebitis occurred in four patients to give a total phlebitis score of 9, significantly higher than in group 1 ($\chi^2 = 4{\cdot}615$, 1 d.f., $P < 0{\cdot}01$). Four of the 17 patients in group 3 required conversion to central feeding, on days 3 (two patients) and 4 (two). In all four patients the most recent infusion had been via the long line. The standard short cannulas in this group created a cumulative phlebitis score of 5, whereas the 24 long lines produced a phlebitis score of 15. Catheter failure and severe phlebitis were seen with significantly increased frequency in group 4 compared with groups 1 or 2 (*Table 3*). In group 4, only six of the 13 patients completed their TPN course as randomized. Of the 24 cannulas used in this group, eight were abandoned because of failure to maintain adequate flow rates despite the use of volumetric pumps, and four because of the development of severe phlebitis. This gave a phlebitis score for group 4 of 12, significantly higher than in either of the groups with short cannulas. Three patients completed their TPN requirements as a 12-h cyclical infusion as in group 1. A further three patients declined to have any further parenteral nutrition.

The number of venepunctures necessary to insert the cannulas was greatest in patients in whom lines were removed after a 12-h cyclical infusion (group 1) and least in those randomized to receive a unilateral fine-bore long line (group 4) (*Table 2*).

Table 3 Cannula survival and complications

	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 17$)		Group 4 ($n = 13$)
No. of cannulas	115	64	50		24
			Short	Long	
Mean duration of cannula survival (days)	—	4·2	3·6	3·2	2·7
Surface area of cannula (mm^2)	176	176	176	660	380
Venous complications					
Mild phlebitis episodes	0	3	2	0	4
Severe phlebitis episodes	0	2	1	5	4
Phlebitis score	0	9*	5	15†	12‡
Venous occlusion	3	2	2	3	8

*$P < 0{\cdot}05$ (group 2 *versus* group 1); †$P < 0{\cdot}05$ (long group *versus* group 1), $P < 0{\cdot}05$ (long group *versus* group 2); ‡$P < 0{\cdot}01$ (group 4 *versus* group 1), $P < 0{\cdot}02$ (group 4 *versus* group 2)

Discussion

The results of this study indicate that the incidence of severe infusion phlebitis is minimized when PPN is administered on a cyclical basis with rotation of venous access sites, confirming previous work from this and other departments[4,10]. Although cyclical infusion with rotation of venous access sites is associated with minimal morbidity, the technique has disadvantages. Not only is it time consuming for the nutrition nurse or doctor to reinsert lines on a daily basis, it is also unpleasant for the patient to be subjected to daily venepuncture[9]. The present study analysed the effect of reducing the number of venepunctures in group 2, where cannulas and PPN infusion techniques were as in group 1, but in whom bilateral cannulas were inserted simultaneously at the start of infusion. Although all patients in group 2 successfully completed the desired duration of parenteral nutrition, there was an increased incidence of phlebitis.

Endothelial damage resulting from a jet of hyperosmolar fluid striking the vein wall has been proposed as a significant factor in the development of infusion phlebitis and occlusion. This has led many researchers to suggest the use of peripheral long lines, which have the theoretical advantage of ensuring greater dilution of nutrient solution on delivery into a vein of larger calibre and higher flow rates than in a forearm vein. It has also been suggested that the cannula tip of a long line floats centrally within the wider lumen, thereby minimizing further mechanical abrasion to the endothelium of the vein[11]. In group 3 the incidence of cannula failure and severity of phlebitis was similar to that in group 2 in veins containing the standard-sized cannula. These complications were encountered with greater frequency in veins harbouring the long catheter. As with patients in groups 1 and 2, this group also received nutrient solutions on a cyclical 12-h basis, standardizing the duration of exposure of the vein to these solutions. As there was no difference between the mean duration over which the short and long cannulas remained within the vein (3·6 and 3·2 days respectively), catheter length appears to be an important factor in the development of these complications.

Other authors have previously reported that 18-G 15-cm cannulas are more likely to be associated with thrombophlebitis[6]. The present study investigated a fourth group of patients in whom a 23-G silicone cannula was inserted into an appropriate forearm vein. Because of the small diameter of the catheter, cyclical infusion was not possible and patients received the nutrient solution over a 24-h period. The results in this group were disappointing, with severe phlebitis and thrombotic occlusion occurring in 12 of the 24 cannulas used. The phlebitis score was also significantly worse in group 4 than in either of the groups with short cannulas.

The discrepancy between the present results and those of others using fine-bore cannulas may be accounted for by the authors' decision to avoid the use of cubital fossa veins, because placement of a cannula across a joint has been said to permit movement of the cannula within the vein during flexion and extension, which can promote endothelial damage. However, the successful results reported by others using fine-bore cannulas, inserted into the basilic or cephalic vein at the cubital fossa, appear to discount this concern[11]. Possibly, the fact that these cannulas are soft and flexible minimizes endothelial damage caused by movement of the arm. Excellent results[5,6] with fine-bore feeding lines inserted at the cubital fossa may be because the tip of the cannula lies in a larger calibre vein, contributing to dilution of infused nutrients. This is supported by previous observations which show clear differences in the incidence of phlebitis with cannulas of similar length but different diameter[8,12].

Damage to the endothelium of peripheral veins during PPN can occur for a number of reasons. First, the injury may be caused by cannula insertion into the vein. The findings of this study suggest that this cause is of little relevance in the development of phlebitis or occlusion, as an inverse relationship was found between the onset of phlebitis and the frequency of venous puncture. Second, endothelial damage might be related to the time for which the cannula remains in the vein. Again, the present results do not support this (*Table 2*). Third, the traumatic effect of infusate striking the vein wall has long been cited as a possible cause of endothelial damage and phlebitis[13]. If this is true, then a segment of vein exposed continuously to such trauma would be more likely to develop inflammation and thrombosis than veins that are rested regularly between infusions. In the only group of patients undergoing a continuous 24-h infusion (group 4), 50 per cent of cannulas failed, either from occlusion or phlebitis, within 72 h of starting flow. All other veins were exposed to 12 h only of infusate and, although this was at a higher flow rate of infusion, these veins were rested for 36 h before re-exposure to infusate. The failure rate of group 4 was significantly greater than that of any of the other three groups, suggesting that duration of infusion may be an important factor in the development of both phlebitis and non-phlebitic occlusion.

Finally, the surface area of prosthetic material to which the vein is exposed may contribute to the degree of endothelial damage sustained. Interactions at the blood–biomaterial–endothelium interface undoubtedly initiate a cascade of cellular events that can bring about vein injury. The standard 18-G cannulas used in this study have a surface area of 176 mm^2. This is considerably less than the surfaces of 376 and 660 mm^2 of the longer catheters used in groups 4 and 3 respectively, the two groups in whom the highest incidence of phlebitis and occlusion occurred. It is interesting to speculate that there may exist a critical ratio of biomaterial area to vein wall area above which a tendency to thrombosis and phlebitis develops.

The incorporation of heparin and hydrocortisone[14] into the infusate and the use of topical glyceryl trinitrate patches[11] have been reported to reduce the incidence of phlebitis during PPN. These methods were not used in the present patients as they were not part of standard line care in the unit, which at the outset of the study was as in group 1. The authors are not convinced that such measures might benefit their patients in view of the low rate of phlebitis in group 1.

There can be little doubt that mechanical trauma plays an important part in the development of infusion phlebitis and occlusion during PPN. This study suggests that the duration of infusion, catheter length and catheter surface area are particularly significant. These factors will be even more important in veins of small diameter.

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British Journal of Surgery 1996, 83, 1095–1100

Glyceryl trinitrate prevents neutrophil activation but not thromboxane release following ischaemia–reperfusion injury

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The aim of this study was to determine whether glyceryl trinitrate (GTN) has a protective effect on neutrophil-mediated lung injury in a model of aortic occlusion (30 min) and reperfusion (120 min). Sprague–Dawley rats were randomized into control ($n = 11$), ischaemia–reperfusion (IR) ($n = 12$), and IR treated with GTN (2 μg kg^{-1} min^{-1}) during reperfusion ($n = 10$). Myeloperoxidase (MPO) activity measured pulmonary neutrophil influx. Pulmonary endothelial permeability was measured by wet:dry weight ratio, bronchoalveolar lavage (BAL) protein and neutrophil counts. Neutrophil superoxide release was measured by flow cytometry in a further IR *versus* GTN experiment ($n = 6$ in each group). The significant increase in MPO activity produced by IR to a level of 7·99 units g^{-1} was prevented by GTN which reduced the level to 4·73 units g^{-1}. The increase in pulmonary microvascular leakage after reperfusion was also prevented by GTN: BAL protein without GTN was 992 μg ml^{-1} and with GTN 579 μg ml^{-1}; BAL neutrophil count without GTN was 3219 cells mm^{-3} and with GTN 820 cells mm^{-3}; the wet:dry lung weight ratio without GTN was 3·8 and with GTN 3·3. Neutrophil superoxide release increased significantly after 40 min of reperfusion in the untreated IR group ($P < 0·05$). This increase was prevented in the GTN-treated group. GTN administration had no effect on plasma thromboxane production during revascularization. These data suggest that GTN administration during the reperfusion phase has the potential to decrease pulmonary microvascular injury.

Continued or accelerated tissue injury following restoration of oxygenated blood flow is a major problem after ischaemia[1]. Neutrophils act as common mediators of this organ injury by local release of reactive oxygen species and proteolytic enzymes[2]. Humoral mediators involved in mediating the systemic inflammatory response to ischaemia–reperfusion (IR) injury include the arachidonic acid metabolites, thromboxane and leukotrienes, components of the complement system (C3a and C5a), and the proinflammatory cytokines, interleukin 1 and tumour necrosis factor. These agents act both directly, by altering endothelial cell cytoskeletal structures and widening interendothelial cell gap junctions, and indirectly, by promoting further neutrophil chemotaxis and activation[3–6]. The end result of this process is pulmonary microvascular endothelial damage causing microvascular protein leakage. The resulting pulmonary dysfunction is characterized by hypoxaemia, pulmonary oedema in the presence of normal left-sided cardiac filling pressures, ventilation–perfusion mismatch and reduced pulmonary compliance[7,8].

Basal endothelial cell production of nitric oxide (NO) is critical to normal vascular homeostasis[9]. Endothelial cells regulate vasomotor tone[10,11], vascular permeability[12] and leucocyte adherence[13] through the production of NO. The ability of endothelial cells to produce NO is decreased during reperfusion[14]. Tao *et al.*[15] demonstrated that NO production is markedly reduced as soon as 2·5 min of *in vivo* reperfusion after 90 min of ischaemia. Administration of NO in the form of sodium nitroprusside before the onset of reperfusion prevents pulmonary architectural damage, and white cell and protein leakage[16]. Glyceryl trinitrate (GTN), currently used to control cross-clamp-induced hypertension during aortic surgery, may have an advantage over nitroprusside in terms of preservation of splanchnic and spinal cord perfusion during cross-clamping[17,18]. The aim of this study was to investigate whether administration of intravenous GTN before the revascularization phase of aortic surgery prevents neutrophil activation and subsequent lung damage in an animal model of aortic occlusion and lower torso reperfusion.

Methods

Animal preparation

Thirty-three adult male Sprague–Dawley rats each weighing 400–500 g were anaesthetized with inhalational halothane. An external jugular venous catheter was inserted for fluid, drug and heparin administration. A carotid arterial line was inserted to monitor systemic blood pressure throughout the procedure using a transducer (model 1290 A OPT 006; Hewlett Packard, Palo Alto, California, USA). Core temperature was monitored for the duration of the experiment using a rectal temperature probe.

In a second experiment 18 animals in three groups of six were used. Venous blood samples were taken from the external jugular vein after induction of anaesthesia and at 5, 40 and 60 min after the onset of reperfusion to assess neutrophil counts, neutrophil respiratory burst activity and plasma thromboxane levels.

In a further experiment venous blood samples were taken from 15 animals in three groups of five at similar time points for plasma NO estimation.

Aortic occlusion and reperfusion

Anaesthetized animals underwent a midline laparotomy. After systemic heparinization (400 units heparin kg^{-1}) the infrarenal aorta was exposed and clamped for 30 min using a microvascular clamp. In control animals the aorta was exposed but not clamped and a saline infusion was initiated after 30 min, lasting 125 min. In the IR group, a saline infusion was commenced 5 min before aortic unclamping and continued throughout the 2 h period of

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Presented to the Surgical Research Society, in London, UK, in January 1994
Paper accepted 5 October 1995

reperfusion. In the third group a GTN infusion was started 5 min before aortic unclamping at a dose of $2\,\mu g\ kg^{-1}\ min^{-1}$ and continued throughout the reperfusion period.

At the end of the experiment the animals were killed with an overdose of anaesthetic. After sternotomy the left main bronchus was clamped. Bronchoalveolar lavage (BAL) of the right lung was performed with 2 ml of saline containing 0·07 mol l^{-1} ethylene diamine tetra-acetic acid and repeated three times. The combined lavage returned was centrifuged at 1500 revolutions min^{-1} for 20 min at 4°C, frozen at −20°C and subsequently assessed for protein concentration.

Wet: dry lung weight ratio

The wet: dry weight ratio of the left lower lobe was calculated after weighing the freshly harvested organ and heating it at 60°C in a gravity convection oven (model IH-150; Gallen–Kamp) over a 72-h period after which time the weight was constant.

Myeloperoxidase assay

Myeloperoxidase (MPO) is a haem-containing enzyme within the azurophil granules of neutrophils. Its measurement has been shown to be a simple quantitative method of detecting leukosequestration. The right ventricle was cannulated using a 25-gauge needle and the right pulmonary hilum clamped. The pulmonary vasculature of the left lung was flushed using 50 ml saline to clear the lung of intravascular neutrophils. After weighing, the left lung was homogenized in 10 ml 0·5 per cent hexadecyltrimethyl ammonium bromide in 50 mmol l^{-1} potassium phosphate buffer at pH 6. The homogenate was freeze-thawed twice and centrifuged at 12 000*g* for 15 min. The resultant supernatant was assayed spectrophotometrically for MPO activity by incubating 0·1 ml of the supernatant with 2·9 ml of a solution containing 2·9 ml of *O*-dioniside dihydrochloride in 90 ml distilled water, 10 ml 50 mmol l^{-1} potassium phosphate buffer (pH 6) and hydrogen peroxide. The change in absorbance with time, at 460 nm, was then recorded (CPU 8720, UV/VIS scanning spectrophotometer; Phillips, Luminar Technology, Southampton, UK). One unit of MPO was defined as that degrading 1 μmol peroxide min^{-1} at 25°C.

Bronchoalveolar lavage

Lung lavage fluid protein content was measured spectrophotometrically using the Lowry method[19]. Neutrophil counts in BAL fluid was carried out by Diff-Quick staining and consecutive counting of neutrophils per high-power field.

Neutrophil respiratory burst activity

Blood was drawn into heparinized tubes and assayed within 4 h. The respiratory burst was assessed using a Bursttest (Orpegen, Heidelberg, Germany). This method allows the determination of leucocyte oxidative and enzymatic activity using dihydrorhodamin 123 (DHR 123) as a fluorogenic substrate, and measures flow cytometrically. Whole blood (100 μl) was incubated alone or with 10 μl rat serum opsonized *Escherichia coli* for 10 min; 10 μl DHR 123 was then added and incubation continued for a further 10 min. Erythrocytes were then lysed by the addition of lysing solution for 20 min. After centrifugation the cell pellets were washed and suspended in 100 μl DNA staining solution. The analysis of respiratory burst activity was performed on a Facscan (fluorescence activated cell sorting) cytofluorometer (Beckton Dickinson, Mountain View, California, USA) detecting mean channel fluorescence. A minimum of 5000 cells was collected and analysed using the software Lysis II (San Hose, California, USA).

Plasma thromboxane

Blood was drawn into tubes containing ethylenediamine tetra-acetic acid and indomethacin, and centrifuged at 2500 revolutions min^{-1} for 15 min. Plasma was separated and stored at −20°C until assayed. Plasma thromboxane was measured by assaying its stable metabolite thromboxane B2 using a radioimmunoassay (Amersham Life Science, Little Chalfont, UK).

Plasma nitric oxide

Blood was drawn into heparinized tubes. NO was measured indirectly by determination of plasma nitrite concentrations. Aliquots of plasma (100 μl) were incubated with equal volumes of Greiss reagent (1 per cent sulphanilimide/0·1 per cent naphthylethylene diamide dihydrochloride/2·5 per cent phosphoric acid) for 10 min at 37°C. Absolute values were determined using nitrite as standard. Absorbance was read at 550 nm on a microplate reader.

Neutrophil counts

Blood was drawn into tubes containing ethylenediamine tetra-acetic acid. After lysing of erythrocytes and centrifugation at 250*g* for 5 min the cell pellets were washed. Cell counts were measured on a Facscan by gating the neutrophil population and calculating the percentage neutrophil count based on a minimum of 10 000 cells counted.

Statistical analysis

Results are expressed as mean(s.e.m.). Results were analysed using one-way analysis of variance for comparison of multiple means with post-hoc Scheffe test analysis. Significance was accepted at the $P < 0·05$ level.

Results

Lung myeloperoxidase activity (*Table 1*)

Ischaemia followed by reperfusion resulted in a significant increase in pulmonary leucosequestration as indicated by an increase in MPO activity. This rise was significantly attenuated by treatment with GTN.

Pulmonary permeability (*Table 1*)

Pulmonary permeability as assessed by BAL protein and neutrophil counts was significantly higher in untreated animals than in control and GTN-treated groups. Likewise, treatment with GTN returned BAL fluid protein content towards control levels, compared with that in the IR group. Wet-to-dry lung weight ratios followed a similar trend to that of the previous results, indicating a higher

Table 1 Effect of 2 h of lower torso reperfusion on parameters of lung injury

	Controls	IR-treated group	IR-treated group given GTN
Lung myeloperoxidase (units g^{-1})	4·54(0·35)	7·99(0·66)*	4·73(0·28)
BAL neutrophil count (cells mm^{-3})	361(102)	3219(1087)†	820(221)
BAL protein content ($\mu g\ ml^{-1}$)	573(102)	992(125)*	579(54)
Wet-to-dry lung weight ratio	3·29(0·08)	3·8(0·20)†	3·3(0·08)

Values are mean(s.e.m.). *$P < 0·01$ *versus* control and GTN-treated groups; †$P < 0·05$ *versus* control and GTN-treated groups (one-way analysis of variance). IR, ischaemia–reperfusion; GTN, glyceryl trinitrate; BAL, bronchoalveolar lavage

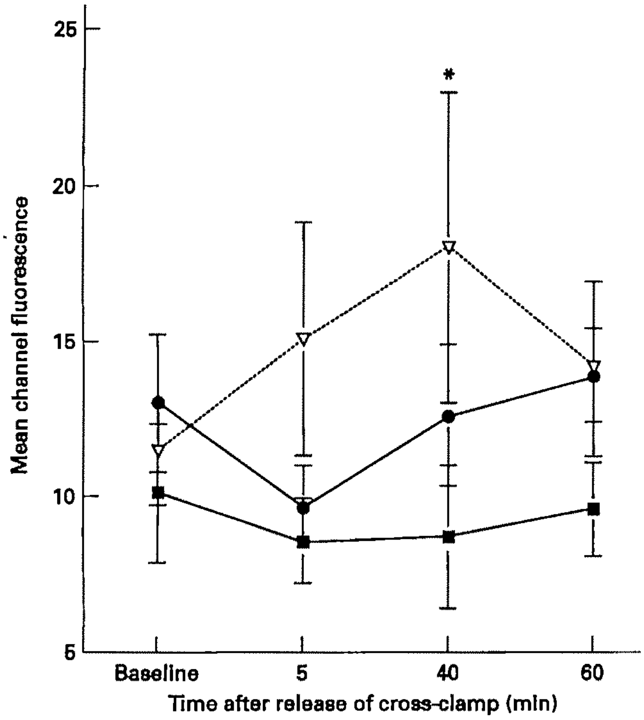

Fig. 1 Effect of ischaemia–reperfusion (IR) on peripheral blood neutrophil activation assessed by neutrophil respiratory burst activity (mean channel fluorescence) in blood samples taken before (baseline) and 5, 40 and 60 min after release of the cross-clamp in controls (■), and animals subjected to IR (▽) and IR treated with glyceryl trinitrate (●). Data are mean(s.e.m.). *$P<0·05$ *versus* baseline and controls at 40 min (one-way analysis of variance)

amount of extravascular lung water in untreated IR animals than in controls and GTN-treated animals.

Neutrophil respiratory burst activity (Fig. 1)

Reperfusion resulted in a significant increase from baseline in neutrophil respiratory burst activity at 40 min in the untreated IR group: baseline 11·42(1·69) and 18·05(4·95) mean channel fluorescence at 40 min ($P<0·05$). In the control group the analagous values were: baseline 10·13(0·18) and 8·7(1·1) mean channel fluorescence at 40 min ($P<0·05$ *versus* IR group at 40 min). There was no significant change in neutrophil respiratory burst activity from baseline in the group of animals treated with GTN: baseline 13·06(2·24) and 12·65(2·3) mean channel fluorescence at 40 min.

Neutrophil counts

The onset of revascularization in the IR group resulted in a transient leucopenia: baseline 37·96(4·95) and 30·74(5·55) percentage of total cells counted at 5 min. This was not observed in either of the other two groups.

Plasma thromboxane (Fig. 2)

Plasma thromboxane levels remained unchanged in the control group before and after the laparotomy incision and for the duration of the experiment: 96·93(10) pg ml^{-1} before clamping and 90·1(15) pg ml^{-1} at 5-min reperfusion; 101(12) pg ml^{-1} at 40-min reperfusion;

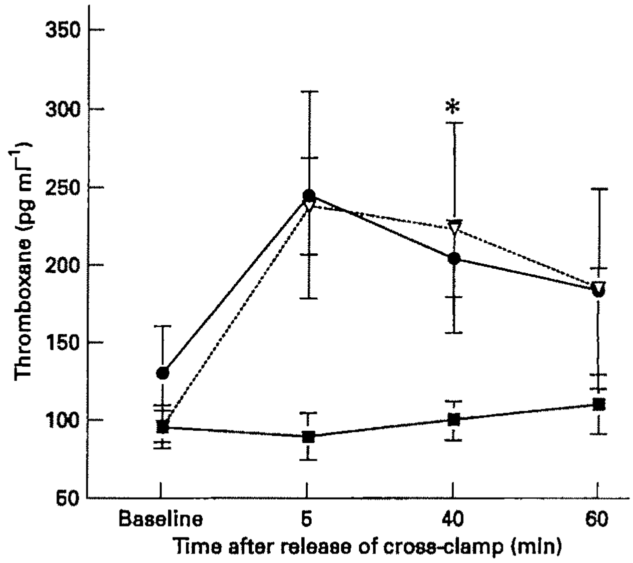

Fig. 2 Plasma thromboxane levels in blood samples taken before (baseline) and 5, 30 and 60 min after release of the cross-clamp in controls (■), and animals subjected to ischaemia–reperfusion (IR) (▽) and IR treated with glyceryl trinitrate (GTN) (●). Data are mean(s.e.m.). *$P<0·05$ *versus* baseline control, IR and GTN groups and controls at 5 min (one-way analysis of variance)

111·2(19) pg ml^{-1} at 60-min reperfusion. In the other two groups, however, levels increased rapidly following the onset of reperfusion: baseline IR 96·66(14) pg ml^{-1} and 224(67) pg ml^{-1} at 40 min ($P<0·05$ *versus* baseline IR and controls at 40 min); baseline GTN 130(31) pg ml^{-1} and 205(24·5) pg ml^{-1} at 40 min and were raised in both groups to 1 h after clamp release: IR 186(65) pg ml^{-1} and GTN 180(68) pg ml^{-1} at 60 min.

Plasma nitrite levels

Plasma nitrite levels were used as an indirect measurement of NO levels. Baseline levels were similar in all groups and remained relatively unchanged throughout the experimental period in the control and GTN-treated animals. However, there was a significant decrease in nitrite levels in the untreated IR group at 5 min of reperfusion: baseline 25·39(1·84) and 18·6(4·18) μmol l^{-1} at 5 min ($P<0·05$ *versus* baseline IR, and GTN-treated and control groups at 5 min). These levels returned towards baseline levels at 15 min: IR 28·48(1·46) μmol l^{-1}.

Systemic mean arterial blood pressure (Fig. 3)

Systemic arterial blood pressure was measured in all groups throughout the duration of the experiment. Revascularization resulted in significant hypotension in the untreated IR group: baseline 102(9·3) and 37·8(12·7) mmHg at 120 min ($P<0·01$). A similar but no more marked decline in systemic blood pressure was seen in the GTN-treated group: baseline 106(10·7) and 51·3(9) mmHg at 120 min.

Discussion

Neutrophil activation has been implicated as one of the key mediators of distant organ damage and dysfunction

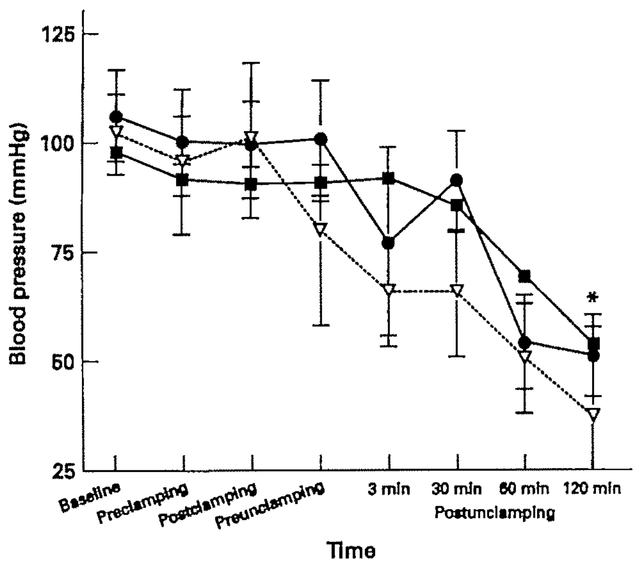

Fig. 3 Systemic arterial blood pressure measured before abdominal incision (baseline), immediately before application of the cross-clamp (preclamping), immediately after cross-clamping (postclamping), before removal of the cross-clamp (preunclamping), and 3, 30, 60 and 120 min after unclamping (postunclamping) in controls (■), and animals subjected to ischaemia–reperfusion (IR) (∇) and IR treated with glyceryl trinitrate (●). Data are mean(s.e.m.). $^{*}P < 0.01$ *versus* baseline IR (one-way analysis of variance)

caused by reperfusion injury[8,20]. The lung is particularly affected by this process. After adhering to pulmonary microvascular endothelium, neutrophils exert their toxic effects through the release of proteolytic enzymes and free radicals[1,20]. Numerous therapeutic modalities have been proposed to counteract this injury, including antioxidants, leucocyte depletion[21], antiproteolytic agents[20] and monoclonal antibodies to specific neutrophil adhesion receptors[22,23]. Recent studies have shown NO to be an important modulator of endothelial cell and neutrophil function[13]. Healthy endothelial cells produce NO which, in addition to its role in the regulation of vascular smooth muscle tone, vasomotor tone and platelet aggregation, prevents neutrophil adherence and activation[24]. NO inactivation by superoxide anion during reperfusion results in local vasoconstriction, and neutrophil and platelet activation and aggregation[25].

The aim of the present study was to determine whether GTN, a NO donor already used routinely during the cross-clamp period of aortic surgery, would have similar beneficial effects when administered before and during limb revascularization. GTN has previously been shown to mimic the action of the endogenous vasodilator NO[26]. NO, produced as an intermediate in the metabolism of GTN by vascular tissue, increases intracellular guanosine 3′5′-cyclic monophosphate (cGMP) resulting in vascular smooth muscle relaxation and vasodilatation[27]. Marks *et al.*[26] have demonstrated increased levels of NO over time following incubation of GTN with bovine pulmonary artery. The beneficial effects of GTN in endotoxin-induced lung injury *in vivo* have been shown by Koizumi *et al.*[28] who demonstrated significant improvements in pulmonary haemodynamics and lung fluid balance. They attributed this mainly to its vasodilatory effect in the pulmonary vasculature.

The results of the present study demonstrate amelioration by GTN of reperfusion-induced lung injury, in a model of aortic occlusion, through prevention of neutrophil activation. In the first part of this study GTN was shown to prevent pulmonary neutrophil infiltration. This supports a role for GTN in maintaining the integrity of the endothelial barrier, through local production of NO, preventing neutrophil adherence, activation and subsequent endothelial disruption. Revascularization in the study described here resulted in significant neutrophil activation as assessed by increased neutrophil respiratory burst activity in untreated animals compared with that in control animals. Similar patterns of neutrophil activation and changes in leucocyte populations in patients undergoing elective aortic aneurysm reconstruction have been reported[29]. Treatment with GTN prevented this neutrophil activation. Comparable effects on neutrophil activation have recently been obtained using other organic nitrates. Sodium nitroprusside administration prevented neutrophil activation and subsequent pulmonary endothelial damage during reperfusion in a model of aortic occlusion and lower torso revascularization[23]. *In vitro* studies using the relatively new nitrovasodilator, nicorandil (*N*-[2-hydroxyethyl]nicotinamide nitrate), have shown that it can inhibit superoxide anion production by activated canine neutrophils in a concentration-dependent manner[30]. Further *in vitro* studies have demonstrated that NO protects vascular endothelium from neutrophil-mediated injury by scavenging superoxide anion produced by activated leucocytes and also by a direct action on a membrane component of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[31].

The onset of reperfusion was associated with a transient decrease in plasma NO levels in the untreated IR group; this effect was not seen in the GTN-treated animals. There was no detectable increase in plasma nitrite levels in response to GTN infusion, probably because of the extremely short half-life of NO and its immediate consumption by endothelial cells subjected to ischaemia. Similar results have been reported by Kurose *et al.*[32] in an experiment in which small intestine was rendered ischaemic for 20 min followed by reperfusion. Plasma nitrite/nitrate levels in superior mesenteric vein samples were significantly reduced after 30 min of reperfusion. These results and those from the present study support the hypothesis that ischaemia–reperfusion injury reduces tissue NO levels, probably as a result of both NO synthase inactivation and superoxide-mediated NO inactivation. The transient leucopenia is consistent with the finding of greater numbers of neutrophils in the BAL fluid. This may explain why the lung tends to suffer disproportionate injury during limb revascularization. Leucopenia was prevented by administration of GTN in this model, indicating a role for NO in preventing neutrophil sequestration in remote organs.

While most experimental data to date indicate that NO modifies neutrophil–endothelial cell interaction directly, its effect on one of the most potent humoral mediators in reperfusion was also investigated. Thromboxane levels have been shown in this and other experimental studies[2,8] to increase rapidly following aortic clamp removal. The release of thromboxane, a potent vasoconstrictor, is temporally related to the onset of pulmonary hypertension during lower torso revascularization[2]. More significantly, perhaps, it or one of its metabolites has also been implicated as a negative inotropic agent, which may contribute to myocardial dysfunction seen in patients undergoing aortic surgery[33]. In the clinical setting GTN is used to produce pulmonary vasodilatation and reduce pulmonary arterial pressure. However, its mechanism of action in the pulmonary microvasculature remains incompletely understood. One mechanism that has been proposed is that GTN-mediated vasodilatation may be partially mediated through an effect on the metabolism of the cyclo-oxygenase products of arachidonic acid metabolism. Levin *et al.*[34] have shown that GTN alone can inhibit thromboxane synthesis and platelet aggregation only in suprapharmacological concentrations, but at clinically attainable concentrations it causes a dose-dependent increase in prostaglandin I_2 synthesis by endothelial cells. Further studies have suggested that GTN, when incubated with vascular endothelium *in vitro* alters the balance of thromboxane/prostaglandin production in favour of prostaglandin I_2 production, thereby acting as a vasodilator and platelet inhibitor[34]. In this study GTN administration had no effect on thromboxane production, with similar increases in thromboxane noted in both treated and untreated groups, suggesting that its vasodilatory role is not mediated through the inhibition of thromboxane release.

This study demonstrates a clear therapeutic effect for GTN on neutrophil-induced lung injury, when administered immediately before lower torso revascularization. Although use of GTN during the revascularization phase did not produce an additive effect on systemic hypotension in this particular model, it would be necessary to ascertain this in the clinical setting before its routine use could be recommended. The potential problem of systemic toxicity with GTN usage during the phase of reperfusion could theoretically be surmounted by administering it locally as an infusion into the ischaemic limb immediately before removal of the aortic cross-clamp. This should stabilize neutrophils activated during the ischaemic phase and prevent their further activation, while avoiding the risk of aggravating reperfusion-induced hypotension.

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British Journal of Surgery 1996, 83, 1100

Short note

Preliminary experience with butyl-2-cyanoacrylate adhesive in tension-free inguinal hernia repair

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This report concerns preliminary experience with the adhesive butyl-2-cyanoacrylate (Indermil; Loctite, Dublin, Ireland) for fixation of the mesh and closure of the external oblique and skin during Lichtenstein inguinal hernia repair.

Surgical technique

The hernia repair proceeds as previously described[1] until the polypropylene mesh has been placed over the posterior wall of the inguinal canal ensuring that there is at least 2 cm medial overlap at the pubic tubercle. The butyl-2-cyanoacrylate adhesive is then applied over the surface of the mesh, avoiding the spermatic cord. The adhesive permeates through the perforations in the mesh thus fixing it to the underlying tissues. Approximately 10 s is allowed for the adhesive to set. The external oblique is approximated by linear traction between forceps and the adhesive applied to the edges and allowed to set. The skin is closed in a similar fashion. Less than 5 ccs of adhesive is required to complete the entire procedure.

Results

Twenty-one patients (twenty men) of median age 59 (range 42–83) years who underwent elective unilateral hernia repair have been treated in this way; 16 hernias were indirect. All procedures were performed under general anaesthesia and intravenous Augmentin (SmithKline Beecham, Brentford, UK) 1·2 g was given before operation.

Four patients did not require analgesia after 12 h and the remaining 17 required no analgesia after the first week. The median duration of follow-up is currently 9 (range 6–12) months. All patients were reviewed initially at 2 months and at 4-month intervals for the first year; they will be reviewed annually for a minimum of 5 years. There have been no early recurrences.

Discussion

The tension-free mesh repair as described by Lichtenstein and Shulman[1] is associated with low infection and recurrence rates[2]. The method described in the present paper is based on this repair but uses tissue adhesive instead of sutures or staples for fixation of the mesh and subsequent wound closure. In general cyanoacrylate tissue adhesives are fast acting and haemostatic, and produce cosmetically satisfactory results when used for skin closure[3,4]. In comparison with other, longer-chain, cyanoacrylate tissue adhesives, the advantages of the short-chain butyl-cyanoacrylate formulation used in this study include its sterility, stability and ease of storage, no risk of tattooing and low histotoxicity[5].

In contrast to mesh fixation with sutures or staples there is no risk of periostitis, muscle ischaemia or accidental injury of the inferior epigastric or femoral vessels. Tissue closure is rapid and without risk of injury to the patient or surgeon. The adhesive also acts as a sterile occlusive dressing.

The use of tissue adhesive for tension-free mesh repair of inguinal hernia has not previously been reported. It provides the advantages of a tension-free mesh repair while avoiding the potential problems associated with use of sutures or staples. Now that the potential of this method of mesh fixation has been established it is planned to perform a prospective randomized trial comparing the long-term results of adhesive mesh repair with those of the traditional sutured technique.

Paper accepted 2 April 1996

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British Journal of Surgery 1996, **83**, 1101–1103

Vitamin D_3 exacerbates intimal hyperplasia in balloon-injured arteries

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Although a high dose of vitamin D_3 is known to cause arterial calcification and degeneration, its effect on intimal hyperplasia has never been studied. The aim of this study was to examine the influence of a moderate supplement of vitamin D_3 on intimal hyperplasia in the balloon-injured rat carotid artery. Forty-four rats had balloon injury to the carotid artery; 22 were given oral vitamin D_3 supplementation (0·25 μg kg^{-1} day^{-1}). Animals were killed at 4 weeks and the carotid arteries were perfusion fixed and assessed morphometrically by means of computerized image analysis of transverse sections. Mean(s.e.m.) intimal area was significantly greater in the vitamin D_3-treated animals than in controls: 0·92(0·05) *versus* 0·71(0·07) mm^2 ($P = 0·02$). The area of the media of both injured and uninjured arteries was not influenced by vitamin D_3 administration. A small dose of vitamin D_3 resulted in significant exacerbation of intimal hyperplasia in this rat carotid artery model and raises the question of the role of dietary vitamin D_3 in restenosis following vascular intervention.

In addition to its well established role in calcium homoeostasis, 1,25-dihydroxycholecalciferol (vitamin D_3) has a variety of other functions, including modulation of cell proliferation and differentiation. For most cell types vitamin D_3 appears to inhibit cell proliferation[1–3], although in the case of cultured vascular smooth muscle cells there is evidence that it stimulates proliferation[4,5]. The proliferation of smooth muscle cells plays an important role in the pathogenesis of both atherosclerosis and intimal hyperplasia[6–8]. Vitamin D_3 may be a significant risk factor in atherosclerosis[9], especially in patients exposed to higher than recommended dietary intake[10] or with individual susceptibility[11]. If vitamin D_3 is a smooth muscle cell mitogen, it may also be important in the pathogenesis of intimal hyperplasia and restenosis following angioplasty. Although previous experimental studies[12–15] have documented the calcification and 'sclerotic' changes induced in the arterial wall by vitamin D_3, its effect on early intimal hyperplasia has never been examined. This is a study of the influence of vitamin D_3 on the intimal thickening seen in the rat carotid balloon injury model.

Materials and methods

Balloon injury

Animal procedures and care were within guidelines laid down by the National Health and Medical Research Council of Australia. Forty-four male Wistar Firth rats weighing 330–380 g underwent balloon injury to the left common carotid artery. Anaesthesia was induced with a mixture of oxygen 1·5 l min^{-1} and nitrous oxide 0·5 l min^{-1} plus 3 per cent halothane, followed by intraperitoneal pentobarbitone 40 mg kg^{-1}. A longitudinal incision was made in the neck and the carotid bifurcation identified. Using an operating microscope an arteriotomy was made in the external carotid artery and a 2-Fr Fogarty balloon catheter (Baxter, Old Toongabbie, New South Wales, Australia) was inserted down to the level of the aortic arch, inflated and withdrawn up the common carotid artery three times to cause de-endothelialization. The catheter was removed and the external carotid artery ligated. The neck wound was closed after ascertaining the patency of the common and internal carotid arteries.

Administration of vitamin D_3

All rats received 40 g kg^{-1} of standard rat chow each day containing approximately 1·75 μg kg^{-1} vitamin D_3. The 22 treated animals received an additional dose of 0·25 μg kg^{-1} day^{-1} (1,25(OH)$_2$-cholecalciferol; Roche Products, Dee Why, New South Wales, Australia) by direct instillation into the pharynx. The additional vitamin D_3 was started 3 days before balloon injury and continued until the arteries were harvested at 4 weeks. Control animals ($n = 22$) were administered with a similar volume of water into the pharynx. Balloon injury was performed, blinded as to which group the rat had been allocated.

Histological preparation

Four weeks after injury, rats were anaesthetized and blood was collected for serum biochemistry. The carotid arteries were perfusion fixed via the aorta at a pressure of 100 mmHg with 0·9 per cent saline (60 ml at 15 ml min^{-1}) followed by 10 per cent buffered formalin (15 ml min^{-1} for 20 min) with the effluent drained via the right atrium. Both injured and uninjured carotid arteries were clamped and ligated at both ends while the formalin was still running. Arteries were removed and stored in formalin for 1 week before sectioning. A 10-mm length from the middle third of the carotid artery was used for sectioning. Two sections, each 5 μm thick, were taken at two separate levels and stained with haematoxylin and eosin. Morphometric measurements were performed using computer-generated image analysis (Chromatic Image Analysis System; Leading Edge, Adelaide, South Australia, Australia) at a final magnification of 64. The areas of intima, media and lumen were measured twice for each section in a blinded fashion. The mean was derived for each artery from the measurements of four sections per artery. The results between the two groups were compared with an unpaired *t* test (Statview 512+Graphics; Abacus Concepts, Berkeley, California, USA); $P < 0·05$ was considered statistically significant.

Results

Vitamin D_3 was well tolerated by all rats and there were no deaths between the time of injury and harvesting. Animals from both groups gained a similar amount of weight. Mean(s.e.m.) total serum calcium level was moderately, but significantly, raised in the vitamin D_3-supplemented group (2·72(0·06) *versus* 2·55(0·06) mmol l^{-1}, $P = 0·02$). Five arteries had thrombosed and were excluded from analysis: three in the treated group and two in controls. The intima was thickened in all the

Paper accepted 4 November 1995

Table 1 Effect of vitamin D_3 on uninjured arteries

	Mean(s.e.m.) area (mm^2)		
	Saline ($n = 20$)	Vitamin D_3 ($n = 19$)	P*
Total	1·84(0·09)	1·99(0·10)	0·30
Media	0·41(0·01)	0·43(0·02)	0·29
Lumen	1·44(0·09)	1·56(0·09)	0·34

*Unpaired t test

Table 2 Effect of vitamin D_3 on injured carotid arteries

	Mean(s.e.m.) area		
	Saline ($n = 20$)	Vitamin D_3 ($n = 19$)	P‡
Intima*	0·71(0·07)	0·92(0·05)	0·02
Media*	0·51(0·02)	0·52(0·01)	0·35
Lumen*	0·85(0·08)	0·71(0·05)	0·13
Total*	2·07(0·07)	2·16(0·04)	0·25
Intima/total†	34·2(3·3)	42·7(2·1)	0·04
Intima/media†	140(14)	177(10)	0·04

Value in *mm^2 or †as a percentage of total or media area. ‡Unpaired t test

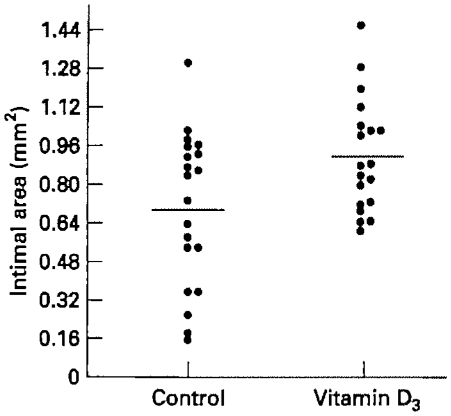

Fig. 1 Distribution of intimal area of the injured artery. Bars represent means

arteries and this was symmetrical in most specimens. Morphometric results are summarized in *Tables 1* and *2*. The distribution of intimal area is shown in *Fig. 1*.

Discussion

The results of the present study show that vitamin D_3 exacerbates intimal thickening in balloon de-endothelialized rat carotid arteries. Whether the intima was compared in absolute values, or as a percentage of the medial area or total arterial area (to correct for differences in the size of the artery), the difference remained statistically significant (*Table 2*).

Intimal thickening is caused by the migration and proliferation of smooth muscle cells and the synthesis of extracellular matrix by these cells[6,7]. The present study did not examine which of these components was affected by vitamin D_3. An increase in smooth muscle cell proliferation is more likely than increased matrix synthesis for a number of reasons. There is *in vitro* evidence that vitamin D_3 stimulates the proliferation of smooth muscle cells[4,5], although one study[16] has shown that proliferation of smooth muscle cells is inhibited. Furthermore, gene expression of the key matrix proteins, elastin and collagen, is repressed in cultured smooth muscle cells by vitamin D_3[17]. Although fibronectin synthesis is stimulated by vitamin D_3[18], it does not contribute substantially to the volume of the matrix[19]. In addition, calcium accumulation in hypervitaminosis D is associated with focal disappearance of collagen and rupture of elastic fibres[14], suggesting breakdown of matrix proteins rather than increased synthesis.

The possibility that changes in calcium levels may have played a role cannot be excluded as the serum calcium concentration in the vitamin D_3-treated rats was raised, although not necessarily into the hypercalcaemic range[20]. There was no evidence in the present study of tissue microcalcification in sections of injured carotid artery, aorta or kidney stained with von Kossa reagent (data not shown). There is some *in vitro* evidence that vitamin D_3 may influence smooth muscle cells independently of any change in calcium level[4]. Smooth muscle cells possess specific cell-surface receptors for vitamin D_3[5,21] and increased smooth muscle cell proliferation was observed at a vitamin D_3 concentration only moderately above physiological levels[4].

The present results support the concept that vitamin D_3 is detrimental to the arterial wall. It is well known that vitamin D_3 in very high doses (25–1000 $\mu g\,kg^{-1}\,day^{-1}$) results in 'arteriosclerosis'[12,14,15]. In most of these studies the arterial damage was attributed to severe hypercalcaemia (total calcium concentration greater than 3·5 $mmol\,l^{-1}$) with clearly demonstrable arterial calcification[12,14,15]. In the present study dietary supplementation with a much lower dose of vitamin D_3 (0·25 $\mu g\,kg^{-1}$), producing only modest rises in serum calcium concentration, exacerbated intimal hyperplasia.

The clinical relevance of this observation needs to be determined. Atherosclerotic changes were reported in the coronary arteries of piglets of sows given vitamin D_3 (25 μg per pound of chow)[22]; blood levels in these animals were similar to those recorded in the American population[23]. Theoretically, hypercalcaemic atherosclerosis induced by vitamin D_3 may be avoided if the daily intake of vitamin D_3 does not exceed 25–30 μg daily in adults[23]. In addition, variable sensitivity to vitamin D_3 has been noted in both experimental and clinical studies. Spontaneously hypertensive rats tolerate vitamin D_3 intoxication better than Wistar Kyoto rats[24]. Hypersensitivity to vitamin D_3 was considered important in cases of supravalvular aortic stenosis seen in children given vitamin D_3 supplementation, and this susceptibility to vitamin D_3 toxicity was thought to be associated with a reduced risk of rickets[11]. There are recent data suggesting that vitamin D_3 receptor gene polymorphism may affect bone density[25]. Further studies are needed to determine the mechanism by which vitamin D_3 affects intimal hyperplasia and the minimum concentration that may exacerbate intimal thickening.

Acknowledgements

This research was funded by grants from the Faculty of Medicine of the University of Western Australia and from the Royal

Australasian College of Surgeons. M.D.L. was supported by the Postgraduate Institute of Sri Lanka.

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Short note

Intraoperative pulse amplitude monitoring of distal perfusion after aortic cross-clamping

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Distal ischaemic and embolic events are well known complications of abdominal aortic surgery. The incidence of these problems is probably underestimated as postoperative monitoring is often limited to examination of foot colour, temperature and pulses. These clinical features are subjective and unreliable[1]. Several monitoring techniques have also been used, including Doppler waveform analysis, ankle : brachial pressure index (ABPI) measurement, pulse volume recording and duplex scanning. None has been accepted universally[2,3]. There remains a need for a simple, inexpensive, reliable method of monitoring distal perfusion. The authors therefore studied the continuous pulse amplitude monitor (CPAM) (Pulse Check pulse amplitude monitor, model 99-0200, sensor model 99-0201; Impra, Tempe, Arizona, USA)[4].

Methods and results

The CPAM uses a disposable transducer, consisting of a piezoelectric polyvinylidine fluoride foil stretched over a compressible foam block, placed on the skin over the dorsal pedal or posterior tibial artery. Skin movement due to the underlying arterial pulsation is detected by the transducer and displayed on a monitor or paper strip.

Thirty-one patients were studied prospectively immediately before and after aortic surgery (*Table 1*). Clinical examination (conforming to the standards of the Society for Vascular Surgery of the International Society for Cardiovascular Surgery[5]), pulse palpation, ABPI measurement and continuous pulse amplitude monitoring were performed. Extra CPAM tracings were obtained immediately before and after cross-clamping, after declamping and after possible reintervention. The CPAM amplitudes were measured and compared with the preoperative amplitude.

In three (5 per cent) of the 62 lower extremities preoperative CPAM tracings could not be obtained because of severe combined central and peripheral occlusive disease; these three patients were excluded from further analysis. Preoperative pulses were not palpable in 18 (30 per cent) of 59 limbs and preoperative ABPI was below 70 per cent in ten (17 per cent) of 59.

Table 1 Patient characteristics and operations

Sex ratio (M : F)	27 : 4
Median (range) age (years)	68 (48–82)
Indication	
Thoracoabdominal aortic aneurysm	8
Abdominal aortic aneurysm	18
Abdominal aortic occlusive disease	5
Operation	
Tube graft	15
Bifurcated graft	16

Immediately after declamping an adequate CPAM waveform was found in 55 feet (true positive). In three feet, initial CPAM tracings after declamping were inadequate, but were improved before closure (temporary false negative). In one patient, insufficient circulation in the foot with persistently inadequate CPAM recordings was found (true negative); following thrombectomy, satisfactory waveforms were obtained. There were no false-positive CPAM results. The mean(s.e.m.) CPAM index was 0·71(0·18) immediately after declamping compared with 0·88(0·14) at the end of the operation ($P = 0·002$, Wilcoxon rank sum test).

Discussion

The distal circulation could be monitored successfully using the CPAM in 95 per cent of cases, whereas clinical examination and ABPI measurement were of limited value. Continuous pulse amplitude monitoring is non-invasive, painless, safe and highly sensitive. It has few disadvantages; it is rather difficult to position the sensor correctly, particularly in occlusive disease, and slight displacement of the probe changes the amplitude of the signal, which negates much of its quantitative value. It is also very sensitive to movement of the patient and the operating table.

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Paper accepted 3 November 1995

British Journal of Surgery 1996, **83**, 1105–1106

Surgical workshop

Endoscopic subfascial division of incompetent perforating calf veins

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Incompetent perforating veins in the medial compartment of the calf are believed to be a major cause of varicose veins in the leg. Cockett and Linton originally described the location of these veins connecting the deep venous system to posterior arch veins and the long saphenous vein, respectively[1,2].

The management of incompetent calf perforating veins remains a therapeutic challenge. Subfascial or extrafascial ligation described by Cockett and Linton has been used for recurrent perforators with or without lipodermatosclerosis[1,2]. These operations have considerable morbidity associated with large incisions through ulcerated areas that heal poorly.

A modified technique of endoscopic management of incompetent perforators which does not include an incision in the gaiter area is described here.

Patients and methods

Patients

Five female patients, median age 66 (range 58–71) years, underwent endoscopic disruption of incompetent perforating veins. Patients were selected by the presence of incompetent perforators in the medial compartment of the leg confirmed on clinical grounds and a duplex scan. On the morning of surgery all patients had a repeat duplex scan to mark the sites of the incompetent perforators.

Surgical technique

Under general anaesthesia the patient was placed supine and the whole limb and groin prepared and draped in the usual manner. Through a groin skin crease incision the saphenofemoral junction was identified, the tributaries ligated and divided, and the long saphenous vein (LSV) disconnected from the femoral vein. The LSV was stripped and retrieved from a small medial incision below the knee. A sterile tourniquet was placed above the knee and inflated above arterial pressure after exsanguination. Through the lower strip incision the subfascial space was developed initially by finger dissection to accept a 10-mm 0° operating endoscope connected to a video endoscopic camera (Storz, Karl Storz GmbH, Tuttlingen, Germany) (*Fig. 1*). Filmy adhesions between the deep fascia and muscle were broken down with blunt dissection employing the endoscope. A modified size 10·5-mm endotracheal tube (Portex Medical, Kent, UK) (*Fig. 2*) in conjunction with the 10-mm endoscope, which allowed a snug fit between the two while permitting free movement of the endoscope, were used to create operating space in the subfascial compartment. Inside the subfascial compartment, the endotracheal tube cuff was inflated to create a space between the fascia and the underlying muscle. Once identified, the perforating veins were either coagulated using modified bipolar diathermy graspers (Storz, Karl Storz GmbH) or clipped if the perforating vein was larger than 3 mm. A specially designed loadable clip applicator was used (Storz, Karl Storz GmbH). Both instruments could be passed through an integral operating channel. The endoscope was passed distally until all perforating veins were identified. A mean of three perforators was identified per patient. In the presence of lipodermatosclerosis, endoscopic fasciotomy was performed using a hook knife (Storz, Karl Storz GmbH). Although not scientifically evaluated, fasciotomy has been used to increase ankle mobility, decrease the risk of compartment syndrome, and reduce the pressure in the deep veins of the calves. At the end of the procedure the groin and below-knee incisions were closed and the limb bandaged.

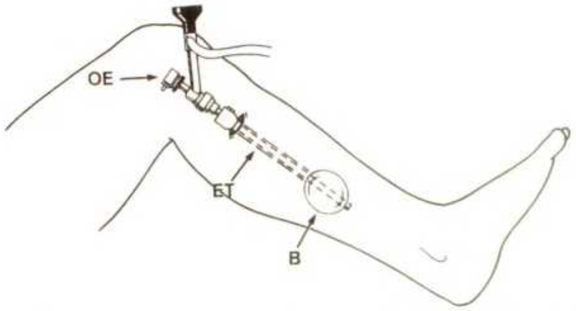

Fig. 1 The technique of insertion of the operating endoscope (OE) surrounded by the modified 10·5-mm endotracheal tube (ET) into an incision on the medial side of the knee. The position of the inflated balloon (B) is also shown

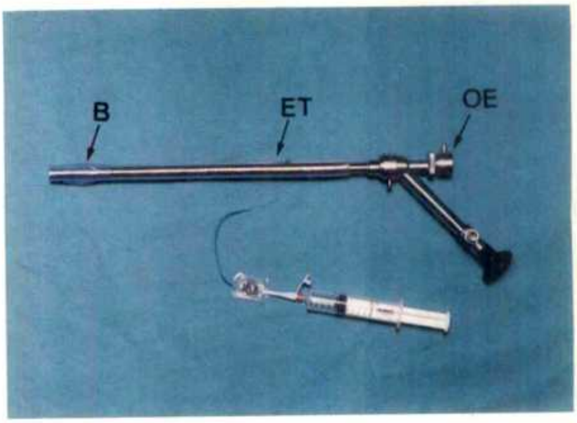

Fig. 2 The 10-mm operating endoscope (OE) placed through the modified 10·5-mm endotracheal tube (ET), together with a syringe to inflate the balloon (B)

Results

All patients were discharged the day after the operation. There was a good clinical resolution of the varicose veins in all cases; median follow up was 6 (range 3–8) months. One patient complained of transient paraesthesia in the distribution of the short saphenous nerve for 2 weeks after surgery.

Discussion

Application of the endoscopic technique in combination with a high saphenous ligation may be useful in both

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Paper accepted 3 October 1995

primary, and particularly recurrent, varicose veins and has been performed in Europe with success. It may also provide new options for the management of venous ulcers[3-5].

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British Journal of Surgery 1996, **83**, 1107–1109

Carotid endarterectomy without angiography

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Between 1 January 1990 and 1 September 1994 a total of 109 carotid endarterectomies were performed without preoperative angiography. Only two cases were considered by the surgeon to have a poor correlation between the duplex examination results and intraoperative findings; the outcome was good in both. The perioperative mortality rate was 1·8 per cent, one patient dying from sudden haematoma causing asphyxia and the other from unrelated causes following a myocardial revascularization procedure. Two non-disabling strokes also occurred. These results suggest that carotid endarterectomy based on carotid duplex scanning alone without preoperative angiography is safe in selected patients.

Duplex scanning has emerged as a safe, non-invasive, accurate method of evaluating patients with extracranial cerebrovascular disease and usually provides complete information about the extent of carotid artery narrowing[1]. On the other hand, because of its invasive nature, contrast angiography is associated with morbidity and mortality which must be added to the overall risk attending surgical intervention[2]. It has been suggested that carotid endarterectomy can be performed safely in selected patients based on the findings of carotid duplex scanning combined with routine cerebral computed tomography (CT) without preoperative angiography[3,4]. When angiography and duplex scanning were compared in the preoperative evaluation of patients being considered for carotid endarterectomy, it appeared that at least two-thirds derived no benefit from the former[5]. After evaluating the accuracy of duplex examination performed by the referring laboratories, the authors started to carry out carotid surgery without preoperative angiography in selected patients. The purpose of the present study is to review experience over the past 4 years.

Patients and methods

Hospital records of all endarterectomies performed without preoperative angiography from 1 January 1990 to 1 September 1994 were reviewed. Demographic data, vascular risk factors, clinical findings, duplex scan results, reasons for conducting surgery without angiography and types of perioperative complications were recorded.

Routine preoperative evaluation included a complete medical history (particularly vascular risk factors), physical and neurological examination performed by an experienced neurologist from the stroke unit, and a brain CT scan. Duplex scanning of the neck arteries was performed by experienced sonographers in two vascular laboratories; their results were validated before commencement of the study by comparing duplex results with conventional angiography in a blinded fashion. A full description of the site, length and width of the plaque, as well as the flow characteristics and degree of stenosis, were required for each patient. The degree of stenosis defined by Doppler ultrasonography was based on established criteria validated specifically for the duplex devices used[1]. All the patients had severe stenosis (greater than 70 per cent) of the internal carotid artery as demonstrated by the duplex study.

Operation was performed under local anaesthesia; a clamping test of the common and external carotid arteries was conducted for 60 s. If any neurological changes were observed during this test, the operation proceeded with shunting. Only in patients regarded before operation as having cardiovascular instability or who were expected to be uncooperative during the procedure was surgery performed with general anaesthesia. If there was any respiratory difficulty or impaired consciousness during the procedure, local anaesthesia was replaced by general anaesthesia.

Results

Of 354 carotid endarterectomies performed during the study period, 109 operations (30·8 per cent) were done without preoperative angiography. The charts of 107 procedures performed on 91 patients were able to be retrieved. The mean(s.d.) age of the patients was 71(8) years. There were 56 men and 35 women.

Vascular risk factors

Sixty-seven per cent of patients had a history of hypertension, 35 per cent had angina pectoris and 32 per cent had experienced a previous myocardial infarction. Fifteen per cent had undergone a previous myocardial revascularization procedure. Thirty-two patients (35 per cent) had diabetes mellitus and 45 (49 per cent) had some form of hyperlipidaemia. Habitual smoking was recorded in 19 per cent. Twenty-four patients (26 per cent) had peripheral vascular disease. Thirteen patients were on a waiting list for a major concurrent operation (generally myocardial revascularization).

Neurological history

Twenty-six patients (29 per cent) were asymptomatic, 26 patients (29 per cent) had had ipsilateral hemispheric transient ischaemic attacks (TIAs), 6 patients (6·5 per cent) had amaurosis fugax, 18 (20 per cent) had had a previous stroke and 9 (9 per cent) had non-specific symptoms (e.g. dizziness); 6 (6·5 per cent) had a combination of these symptoms.

Reasons for surgery without angiography

Two patients had renal insufficiency, seven were known to be allergic to contrast material and 19 needed urgent

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Paper accepted 28 November 1995

operation. In addition, 79 procedures (72 per cent) were performed without preoperative angiography according to the surgeon's preference.

Operations

Most procedures (84 per cent) were performed under local anaesthesia. Mean(s.d.) clamping time for non-shunted procedures was 11·7(3·6) min; for six procedures in which a shunt was used it was 8·4(5·8) min. Mean(s.d.) shunting time was 9·9(5·3) min.

In only two cases was there a discrepancy between operative findings and the duplex scan results. There was total occlusion of the internal carotid artery in one patient with renal failure whose duplex scan showed 99 per cent stenosis (there was a time interval of 26 days between the ultrasonographic examination and operation). In the other patient the duplex scan missed a kink of the internal carotid artery which required a non-planned reimplantation of the artery. The final outcome of these two patients was good.

Perioperative complications

There were 14 intraoperative transient neurological events without any subsequent complications. Of 107 procedures, two patients had postoperative non-disabling strokes (stroke rate 1·8 per cent). One of these patients had a contralateral cerebellar infarction and the other suffered from aphasia and embolization to the retinal artery. Both had only minimal residual deficit after 1 week.

Eight patients developed symptoms that could be related to the hyperperfusion syndrome: four suffered from severe headaches, three had postoperative seizures and one a small intracerebral haemorrhage without neurological deficit.

Two patients died in the immediate postoperative period (mortality rate 1·8 per cent), one on the second postoperative day from asphyxia caused by a neck haematoma which appeared suddenly after discharge from hospital. This patient, like all those undergoing carotid surgery, had received 100 mg aspirin daily throughout the perioperative period. The other patient died several days after coronary artery bypass which followed the carotid endarterectomy; the death was considered to be unrelated to the cerebral revascularization procedure.

Discussion

This study indicates that carotid endarterectomy can be performed safely without angiography using standardized duplex criteria for patient selection. Cerebral arteriography is associated with a risk of neurological, systemic and local complications. In a recent report[2] there was a total complication rate of 3·4 per cent following angiography in patients considered for carotid endarterectomy (1·3 per cent had permanent stroke). Hankey *et al.*[6] in 1990 suggested that the total risk of neurological complications (TIAs or minor stroke) is about 4 per cent and that permanent neurological deficit (disabling stroke) occurs in about 1 per cent. Carotid endarterectomy without preoperative angiography in selected patients may reduce the total morbidity and mortality associated with the operation.

Duplex scanning is the most well established non-invasive modality for evaluation of stenosis at the carotid bifurcation. The sensitivity of colour-flow duplex scanning in assessing internal carotid artery stenosis was suggested as 98 per cent for stenoses greater than 50 per cent in a recent study[7]. The anatomical details are satisfactorily outlined and the duplex study can provide additional important information, such as haemodynamic data and plaque morphology. The ability to characterize the relative proportions of fatty, fibrous and calcific material within the lesion is a significant advantage of duplex technology[4]. The echolucent irregular plaques which this technique reveals are more frequently associated with cerebral ischaemic events; it also provides evidence that these plaques are unstable and tend to embolize[8].

Appropriate application of duplex technology is limited by its dependency on the skills and experience of the sonographer. In the present study examinations were performed in two vascular laboratories at which results were validated before commencement of the research. The technology is not capable of imaging the intracranial and aortic arch circulations, but routine cerebral CT scans done before operation can identify arteriovenous malformations, aneurysms and tumours greater than 1 cm in diameter. The present authors believe that CT is necessary to exclude such other intracranial disease. It also allows the operation to be delayed if a recent infarct is found and serves as a baseline examination to assist management of possible postoperative neurological complications.

Another limitation of duplex scanning is its inability to detect carotid siphon disease. It has been shown, however, that most patients undergoing carotid endarterectomy in the presence of a siphon stenosis are relieved of symptoms without additional risk[9]. Existing carotid siphon disease (tandem lesion) should not preclude the correction of carotid bifurcation pathology.

Doppler ultrasonography is known to be inaccurate in differentiating a totally occluded from a nearly occluded internal carotid artery[10]. In one of the present patients, duplex examination findings were interpreted as tight stenosis but total occlusion of the internal artery was found during operation. The possibility that the total obstruction occurred during the period between the examination and operation cannot be excluded. A recent study has shown that the new generation of colour-flow duplex ultrasound scanners provides an accurate method of diagnosing carotid artery occlusion in most patients[11]. However, given the marked difference in clinical management between patients with high-grade stenosis (surgery) and those with total occlusion of artery (non-surgical treatment), angiography should be carried out in patients with symptoms in whom the duplex results are interpreted as 'possible occlusion'.

The contention that carotid endarterectomy can be performed safely in selected patients based on carotid duplex scanning alone is supported by the surgical outcome. The present results are similar to those of others. A summary of nine published studies has described incidences of 1·4 and 0·6 per cent respectively for perioperative stroke and TIA[4]. The same review reported an incidence of 2 per cent for perioperative neurological events. Another recent study[12] of 130 operations performed without angiography reported an incidence of 1·5 per cent for perioperative TIA, 2·3 per cent for stroke and 1·5 per cent for death. One small series of 47 similar operations did not report any neurological morbidity or mortality[13]. A 1994 study[14] of the results of 110 operations reported a mortality rate of

0·7 per cent from stroke and an incidence of 2·6 per cent for TIA. The present series had a surgery-related mortality rate of 1 per cent (one of 91 patients), the death being unrelated to the preoperative method of evaluation. In conclusion, all these results support the safety of carotid endarterectomy in selected patients based on strict carotid duplex scanning criteria without preoperative angiography.

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British Journal of Surgery 1996, **83**, 1110

Surgical workshop

Modified technique for double stapling of colorectal anastomosis following low anterior resection

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The standard stapling technique for rectal reconstruction following low anterior resection requires that the distal rectum be closed with a linear stapler and the anastomosis created using a circular stapling device that crosses the linear staple line (double stapling technique)[1]. Although there are theoretical concerns about complications arising from intersecting staple lines, these have not materialized in practice[2]. However, remnants of the linear staple line will remain at both corners of the rectal stump. These corners, like dog ears, may be a weak point and the source of anastomotic leakage. A new technique that removes the linear staple line completely is described.

Surgical technique

The sigmoid colon and rectum are mobilized through a lower midline laparotomy. A 50-mm linear stapler (Ethicon, Somerville, New Jersey, USA) is used to transect the sigmoid colon more than 10 cm proximal to the primary lesion. A right-angled clamp is placed at the rectum 2–3 cm distal from the primary lesion and the lumen is washed out using 2000 ml saline. This washout is necessary to clear residual faecal content and to remove any desquamated neoplastic cells. The TL-30 stapler (Ethicon) is placed distal to the right-angled clamp and fired. The rectum is transected with a scalpel immediately proximal to the stapler, which is then released and removed. The sigmoid colon stump is opened, and a purse-string suture is placed using 2/0 polypropylene. The appropriately sized cartridge (detachable curved intraluminal stapler (CDH); Proximate ILS; Ethicon) is selected (usually 33-mm CDH), the detachable anvil is inserted gently into the sigmoid colon and the purse-string suture is tied over the anvil shaft. The CDH instrument is introduced into the rectal segment through the anus. The trocar is extended to penetrate through the centre of the rectal wall immediately adjacent and posterior to the TL-30 staple line. One suture of 3/0 silk on an atraumatic needle is inserted from one corner of the staple line to the other corner (*Fig. 1a*). The suture is tied roughly over the trocar, because the object of this procedure is only to remove the linear staple line completely (*Fig. 1b*). The trocar is then connected to the detachable anvil shaft within the sigmoid colon. The instrument is closed and fired. The instrument is then opened, disengaged from the anastomosis and removed. The doughnuts (central cores of the anastomosed tissues) are inspected to ensure that complete circles of tissue and the linear staple line have been obtained.

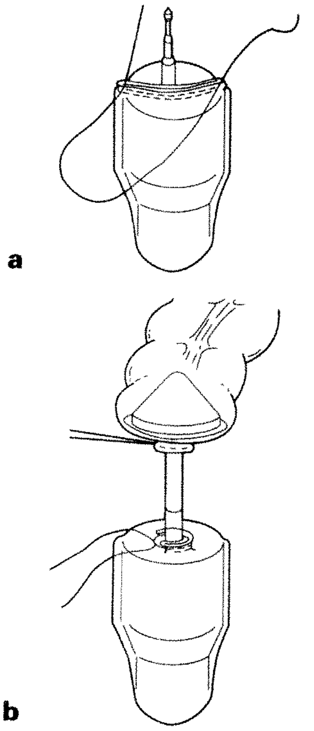

Fig. 1. Modified double stapling technique for rectocolic anastomosis following low anterior resection. **a** A single 3/0 silk suture on an atraumatic needle is inserted from one corner of the staple line to the other. **b** The suture is tied roughly over the trocar

Discussion

Anastomotic leakage is the most serious perioperative complication following low anterior resection. The incidence of anastomotic leakage was 4·4 per cent in a meta-analysis of ten series including 1483 patients[3]. In the authors' series, four of 42 patients who underwent low anterior resection using the standard double stapling method suffered anastomotic leakage. The leak point was identified as being a corner of the linear staple line by contrast study in all four patients. It is quite likely that the everted corners are vulnerable to increases in luminal pressure. Sato *et al.*[4] reported the method of complete resection of the linear staple line. They tied the suture tightly over the trocar. However, with their method several folds, which cause uneven wall thickness, appear around the trocar. Thus, the present authors tied the suture roughly over the trocar because this procedure is only to remove the linear staple line. This new procedure was performed in 20 patients with no anastomotic leaks. These patients underwent the same procedures for low anterior resection as the previous 42 patients except for complete resection of the linear staple line. This modified double stapling technique may be useful following low anterior resection.

Paper accepted 16 November 1995

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British Journal of Surgery 1996, **83**, 1111

Short note

Sengstaken tube for bleeding rectal angiodysplasia

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A new method to control rectal bleeding is presented.

Case report

A 75-year-old woman underwent cervical laminectomy (C3–7) for cervical myelopathy. On day 3 after operation she suffered a myocardial infarction and developed pulmonary oedema. On day 7, she began to pass large amounts of fresh blood from the rectum. There was no previous history of rectal bleeding, altered bowel habit or diverticular disease. Results of routine haematological investigations, including clotting studies, were normal. At sigmoidoscopy there were fresh blood clots in the lumen but no bleeding point was identified.

Persistent haemorrhage necessitated transfusion with 10 units of blood and mesenteric angiography revealed a localized bleeding point in the lower third of the rectum with no other vascular abnormality (*Fig. 1*). A Sengstaken tube was inserted into the rectum and the gastric balloon inflated with 350 ml of air (*Fig. 2*). Haemorrhage immediately ceased and the patient tolerated the balloon well. The balloon was left in place for 48 h with 5 min deflation each hour. There was no rebleed from the rectum and no further rectal bleeding up to 1 month follow-up.

Paper accepted 18 November 1995

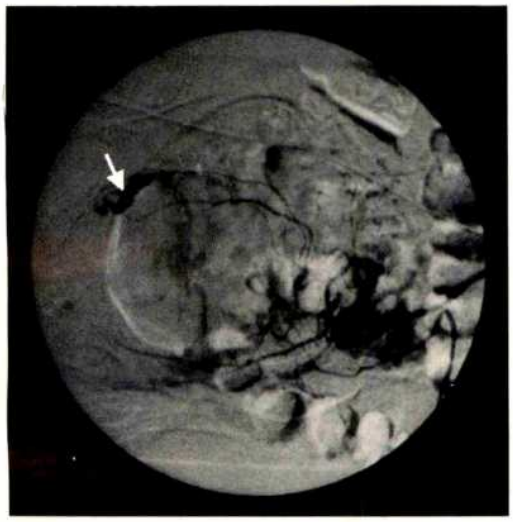

Fig. 1 Mesenteric angiogram showing bleeding angiodysplasia in the rectum (arrow)

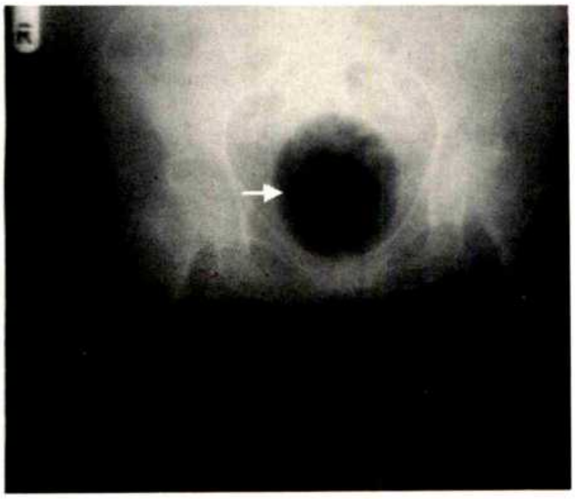

Fig. 2 Abdominal radiograph of inflated Sengstaken tube in the rectum (arrow)

Discussion

Significant rectal bleeding in the elderly is often due to angiodysplasia and, in the absence of other demonstrable pathology, this was the presumptive diagnosis made, although there were no typical angiographic features. Although angiodysplasia is most often located in the right colon[1,2], as many as 25 per cent of lesions are in the left colon and rectum.

In three-quarters of patients admitted with gastrointestinal haemorrhage, bleeding will stop with conservative measures[3]. In the face of continued haemorrhage, there is a choice between visceral angiography or laparotomy with, or without, antegrade colonic lavage and on-table colonoscopy[4,5]. Angiography is the preferred option as it may allow treatment by selective arterial infusion of vasopressin or by embolization of the bleeding site, when accurately identified.

Once the rectum has been found to be the source of the haemorrhage, proctoscopic or sigmoidoscopic fulguration of the bleeding point may be possible. This may be difficult if the haemorrhage is brisk or if there is no raised mucosal lesion. The patient may need to be transferred to the operating theatre and require general anaesthesia. In contrast, a Sengstaken tube is readily available, easily introduced into the rectum and appears to be well tolerated. The Sengstaken tube offers an alternative method of controlling rectal bleeding, particularly in patients not fit for general anaesthesia.

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British Journal of Surgery 1996, **83**, 1112–1115

Pathological evidence in support of total mesorectal excision in the management of rectal cancer

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Some 50 total mesorectal excision specimens were examined following rectal excision for cancer. Circumferential margin involvement was rare, but mesorectal tumour deposits were present in 17 of 44 patients with pT_3 tumours, and 23 of 44 had mesorectal nodal involvement. No patient with a pT_2 tumour had mesorectal involvement. Failure to excise the mesorectum completely has the potential to leave gross or microscopic residual disease that may in theory predispose to local failure. Total mesorectal excision is necessary to avoid incomplete pathological evaluation of the mesorectum and understaging of rectal cancer.

Pelvic recurrence following conventional rectal resection for cancer is common, with a worldwide incidence of approximately 30 per cent for tumours that have penetrated the rectal wall (pT_3), irrespective of nodal status[1,2]. Preoperative irradiation has been shown in prospective randomized studies to halve this risk, although no survival benefit has yet been demonstrated[3,4]. Conversely, the Gastrointestinal Tumor Study Group (GITSG) trial[5] and the North Central Cancer Treatment Group (NCCTG) trials[6] have shown that a combination of postoperative radiation therapy and chemotherapy significantly decreases pelvic failure rate and increases the overall survival rate, and this has become the recommended standard of care for patients with pT_3 N_{0-2} tumours[7].

Although these high local failure rates can be significantly improved upon with adjuvant therapy, there is increasing opinion that many local recurrences are due to incomplete excision of the mesorectum or breach of the mesorectum during rectal resection[8]. The rectum and mesorectum, enveloped by the visceral layer of the pelvic fascia, is a distinct anatomical unit within the pelvis, wherein virtually all regional spread of disease is found. Total mesorectal excision (TME), accomplished by sharp dissection under direct vision along a plane that separates the parietal from the visceral layers of the pelvic fascia, completely excises this unit[9]. Conventional resection is usually performed by blunt dissection along the visceral plane of pelvic fascia, where violation of the mesorectum is probably a common event. Moreover, surgeons seeking 2–3 cm of distal mural clearance may breach the mesorectum just below the tumour and leave behind the distal mesorectum[10]. Heald *et al.*[11] in 1982 first reported a case of mesorectal deposits in the distal mesorectum and cautioned that failure to perform TME may predispose to local failure. This contention was supported in 1993 when Heald and co-workers reported an overall 5-year local failure rate of 5 per cent in 135 patients with pT_3 rectal tumours who had undergone TME in combination with rectal excision[12]. None of these patients received adjuvant treatment.

TME has been the standard operation of the present authors for rectal cancer for approximately 10 years, with a pelvic recurrence rate approaching 6 per cent. Over the past 2 years TME has been combined with a detailed assessment of the mesorectum in all cases. The median follow-up of this group is 18 months and it is premature to evaluate the clinicopathological analysis in terms of local failure. Collaboration between surgeons and pathologists in the authors' unit has led to this detailed pathological study, which provides data to support the case for TME in rectal cancer resection.

Patients and methods

Pathological resections from 50 consecutive patients with biopsy-proven adenocarcinoma of the rectum within 12 cm of the anal verge who underwent curative resection incorporating TME were examined. Some 38 had TME as a component of a low anterior resection and 12 with abdominoperineal resection. 'Cure' was defined as absence of metastatic disease and the excision of all macroscopic tumour tissue with negative proximal and distal margins. TME was performed as described by Heald *et al.*[11]. All patients undergoing low anterior resection thus had an anastomosis at approximately 3 cm from the anal verge, irrespective of the level of the primary tumour.

The resected specimen was examined by one of two pathologists. The fresh specimen was opened on the antimesenteric border or, where the lesion was anterior, lateral to the tumour. The rectum and mesorectum were pinned flat to a cork board, and fixed in 10 per cent formal saline. No fat-clearing techniques were utilized. Serial transverse sections were made at 5-mm intervals through the tumour, bowel wall and mesorectum in continuity, as described by Quirke *et al.*[13]. The surface area and thickness of the tumour were measured, along with grade (well, moderately well or poorly differentiated) and margin (pushing or infiltrative). The presence of vascular, lymphatic and perineural invasion was recorded. Proximal and distal resection margins were inspected.

The mesorectum was evaluated for lymph nodes and tumour deposits in three areas: deep to the tumour, in the proximal mesorectum and in the distal mesorectum. Mesorectal deposits were defined as discrete foci of adenocarcinoma, discontinuous from the primary tumour, with no evidence of nodal tissue. Sections were also examined microscopically for circumferential resection margin involvement. The distance from the outermost aspect of the tumour or tumour deposit was recorded as the circumferential resection margin. All specimens were assigned a Dukes[14] and tumour node metastasis (TNM)[15] stage.

Statistical significance was determined by χ^2 analysis with Yates' correction.

Results

Dukes and pTNM staging is shown in *Table 1*. Six patients had Dukes A lesions. Of 21 patients with Dukes B tumours, five had discrete foci of adenocarcinoma in the

Paper accepted 28 October 1995

Table 1 Pathological characteristics according to Dukes and tumour node metastasis classifications

TN	No. of patients	Dukes stage
T_2N_0	6	A
T_3N_0 (Mr −)	16	B
T_3N_0 (Mr +)	5	B
T_3N_1 (Mr −)	10	C
T_3N_1 (Mr +)	3	C
T_3N_2 (Mr −)	1	C
T_3N_2 (Mr +)	9	C

Mr +/− denotes the presence or absence of apparent non-nodal foci of adenocarcinoma (mesorectal deposits) within the mesorectum

Table 2 Incidence of involvement of mesorectal nodes and deposits in the mesorectum proximal, deep and distal to the tumour in 44 patients with pT_3 tumours*

	Node positive	Deposit positive
Proximal	16	9
Deep	21	16
Distal	9	6

*Overall, 23 patients had involved mesorectal nodes and 17 had involved tumour deposits; 12 had involved distal mesorectum

mesorectum (mesorectal deposits) with no evidence of lymph node metastasis. Dukes C lesions were more heterogeneous, but 12 of 23 patients had distinct mesorectal deposits in addition to mesorectal node involvement. The median distal resection margin was 2·3 (range 0·5–5·0) cm and the median circumferential resection margin was 1 (range 0–4) cm. Two specimens (4 per cent) showed circumferential margin involvement microscopically, both from mesorectal nodules in patients with extensive mesorectal nodal and extranodal disease.

Of six patients with pT_2 tumours, a median of 18 (range 3–24) mesorectal lymph nodes were retrieved. No involved mesorectal nodes or deposits were identified. A median of 20 (range 6–54) mesorectal lymph nodes were retrieved from patients with pT_3 tumours. In marked contrast to those with pT_2 tumours, 28 of 44 patients with pT_3 lesions had involved nodes or deposits ($P<0{\cdot}05$). The number of patients with involved deep, proximal or distal mesorectal nodes or deposits is shown in *Table 2*. In the majority of cases mesorectal involvement was present deep to the tumour. In 12 patients, however, the distal mesorectum was involved, and in one a mesorectal deposit was retrieved 5 cm distal to the lower mural tumour margin. In five of these 12 cases mesorectal involvement was more than 2 cm below the distal mural tumour. In five cases overall, mesorectal deposits were identified in the absence of mesorectal node involvement.

The correlation between mesorectal involvement with nodes or deposits in patients with pT_3 tumours and maximum tumour dimension, tumour thickness, borders, lymphatic, vascular or perineural invasion is shown in *Table 3*. (All but four patients had moderately well differentiated tumours, precluding statistical analysis.) There was a significant association between mesorectal involvement and maximum tumour diameter greater than 5 cm, infiltrating borders, and vascular, lymphatic and perineural invasion. Tumour thickness did not correlate with mesorectal involvement.

Table 3 Correlation between variables in 44 patients with pT_3 tumours

	Mesorectal nodes or deposits			
	Involved ($n=28$)	Tumour free ($n=16$)	χ^2	P
Vascular invasion				
Present	13	0	8·4	<0·01
Absent	15	16		
Lymphatic invasion				
Present	12	0	7·4	<0·01
Absent	16	16		
Perineural invasion				
Present	11	0	6·4	<0·02
Absent	17	16		
Tumour borders				
Infiltrating	20	5	5·1	<0·05
Pushing	8	11		
Maximum diameter (cm)				
>5	20	5	5·1	<0·05
<5	8	11		
Tumour thickness (cm)				
>1·5	17	5	2·4	0·1
<1·5	11	11		

Discussion

There is increasing evidence that a detailed pathological evaluation of the mesorectum, rarely reported and probably rarely performed, is worthwhile and can be used as an audit tool. First, it may predict local recurrence: using sequential transverse whole-mount sections of the tumour and mesorectum, Quirke *et al.*[13] reported in 1986 that local failure in patients undergoing conventional rectal resection was related to microscopic spread beyond the circumferential (lateral, radial, deep, mesorectal) resection margin; 85 per cent of patients with circumferential margin involvement developed local recurrence, compared with 3 per cent of those with negative margins. In a recent update from the same group[16], 23 (40 per cent) of 58 patients with circumferential margin involvement developed a local recurrence compared with nine (8 per cent) of 115 with clear margins. Second, mesorectal analysis may challenge previous dogma: Heald *et al.*[11] identified nests of adenocarcinoma in the distal mesorectum of five patients, three of which were greater than 2 cm distal to the extramural tumour. These authors cautioned that lymphatic distal mesorectal spread, contrary to previous reports[17], may exceed mural spread and that transecting the mesorectum 2 cm below the tumour may leave residual disease. Scott *et al.*[18] recently confirmed that distal mesorectal spread often exceeds intramural spread, and reported the presence of tumour in the distal mesorectum in four of 20 patients who underwent TME. Finally, mesorectal analysis may reveal findings of independent prognostic significance: Cawthorn *et al.*[19] demonstrated that mesorectal invasion (greater than 4 mm) was associated with significantly decreased survival in patients with Dukes B or C tumours compared with patients with minimal (less than 4 mm) mesorectal spread.

The prognostic significance of foci of tumour deposits within the mesorectum is unknown. It is possible that they represent completely replaced lymph nodes. Mesorectal deposits are not incorporated in any current staging nomenclature and the present analysis highlights some of the weaknesses of available classification systems. The heterogeneity of Dukes B and C lesions is evident. Heald and colleagues, in their original series[11] reported that two of five patients had discrete non-nodal mesorectal deposits without evidence of lymphatic or lymph node invasion. This was observed in five patients in the present study, and these tumours would strictly be classified as Dukes B lesions, although such mesorectal deposits would almost certainly carry a worse prognosis than Dukes B tumours without deposits. Dukes C tumour is a composite of many pTNM groups of different prognosis; the incorporation of mesorectal deposits would substantially increase its complexity. Deposits were generally seen in patients with pN_2 disease, and it is less likely in this group that mesorectal deposits have independent prognostic significance.

There is increasing opinion recommending incorporation of an assessment of local residual disease, a so-called 'R' classification (R_0, none; R_1, microscopic residual disease; R_2 macroscopic residual tumour) into clinicopathological staging nomenclature[20,21]. Residual disease, even microscopic residual disease in the line of resection, carries a prognosis not significantly better than that associated with metastatic disease[21,22]. It can be argued that the excellent clinical results obtained with TME are due to elimination of a common site of R_1 or R_2 disease. The present data may support this theory. One potential site is the circumferential resection margin. The Leeds study[16] showed that 25 per cent (35 of 141) of patients undergoing conventional resection had an involved circumferential margin, whereas this was evident in only 4 per cent (two of 50) of patients in the present TME series. The other potential site for residual disease is the distal mesorectum. Although intramural involvement rarely extends distally beyond 2 cm, enabling 'close-shave' sphincter-saving resections with respect to mural clearance[23], the distal mesorectum in the present series was involved by lymph nodes in nine of 44 patients with T_3 tumours and by foci of adenocarcinoma in six of 44. Conventional rectal resection leaves a variable amount of distal mesorectum in the pelvis, and the chance of spillage of viable cells is probably greater when the mesorectum is cut close to the tumour[24]. Blunt dissection is a common component of conventional resection, most usually along the visceral plane of the pelvis fascia, and violation of the mesorectum may occur, particularly at the point of resistance encountered at the rectosacral fascia. Discontinuous mesorectal deposits have previously been described between 2 and 4 cm below the main tumour mass[11]. This has been confirmed in the present study, and in one case a deposit was present 5 cm below the main tumour mass. These data support the rationale for TME and low anastomosis for rectal tumours below the peritoneal reflection, including high mid-rectal tumours, despite the greater potential for perioperative complications and risk of functional problems.

Surgeon variability in local recurrence rates is considerable, suggesting that a uniform operation is not performed for rectal cancer[25,26]. The complications and cost of adjuvant therapy are not inconsequential and if TME becomes the new standard of operation, the indications for adjuvant therapy may need to be reconsidered. The authors consider that failure to make detailed pathological assessment of the mesorectum may overlook nodes or deposits and understage disease, and that failure to perform TME may potentially leave residual disease in the distal mesorectum or at the circumferential margin and predispose to pelvic recurrence.

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British Journal of Surgery 1996, 83, 1116–1120

Prognosis after surgery in patients with incurable rectal cancer: a population-based study

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In a defined population between 1973 and 1992 151 patients with irresectable metastatic or local rectal cancer were identified. Eighty-one patients underwent resection of the primary tumour (group 1) whereas the primary tumour was left *in situ* in 70 patients (group 2). During the same time period, 444 patients underwent curative resection. The median survival was 7·5 months in group 1, and 3·5 and 1·9 months for surgically and non-surgically treated patients respectively in group 2. A colostomy for intestinal obstruction became necessary in 12 per cent of the patients with a retained primary tumour. Bilateral hepatic involvement, abnormal liver function test results, peritoneal growth or abdominal lymph node metastases correlated with a short survival ($P<0\cdot01$). These results support a selective approach to patients with incurable rectal cancer.

Approximately 35 per cent of all colorectal carcinomas are located in the rectum. At the time of diagnosis more than one-third of these tumours are incurable, either because of irresectable local disease, irresectable metastases and/or advanced age or concomitant disease[1]. There have been few studies of the management of patients with incurable primary carcinoma of the rectum. Palliative resection of the primary tumour has been advocated to avoid obstruction, bleeding, tenesmus and pain[2–4], although the proportion of patients who develop distressing symptoms from the primary tumour is not known. However, increased postoperative morbidity and mortality may outweigh any beneficial effects, and life expectancy may be short in some patients. Identification of factors that influence the prognosis may thus be of value in clinical decision-making. Knowledge of the postoperative course and the risk of intractable symptoms from an unresected primary tumour may also aid in planning treatment.

The primary aim of this study was to assess the outcome after surgical and non-surgical treatment of incurable rectal tumours in a defined population. Secondary aims were to identify variables that influence survival, and to analyse the natural history of unresected rectal adenocarcinoma.

Patients and methods

Study population

The records of 927 patients suffering from rectal cancer in the province of Uppsala between January 1973 and December 1992 were identified from the Swedish Cancer Registry. Seventy patients had a non-malignant polyp, 74 carcinoma *in situ* and 72 tumours other than rectal adenocarcinoma (anal cancer, 49; carcinoid, 15; malignant melanoma, three; gynaecological tumour, four; sigmoid adenocarcinoma, one); they were therefore excluded from the study. Five patients were excluded because at the time of diagnosis they were not living in the province of Uppsala, and 37 because the diagnosis was made at autopsy. Finally, 32 patients (3 per cent) were excluded because their records could not be retrieved. This left 637 patients eligible for the analysis. Of these, 151 patients (24 per cent) had surgically incurable disease at the time of diagnosis or surgery and form the basis of this report. Eighty-one patients underwent resection of the primary tumour (group 1), whereas the primary tumour was left *in situ* in 70 (group 2) (*Table 1*). Curative resection was performed in 444 patients who constituted a reference group (group 3). Forty-two patients did not undergo surgery despite the absence of known metastases (group 4). Radiotherapy was given to three in the latter group. The natural course of rectal carcinoma left *in situ* was analysed in these patients as well as those in group 2. Complete follow-up information, i.e. survival, hospital files and pathological records, was available in all these patients.

Treatment

Thirty-six patients in group 1 had abdominoperineal resection, 37 underwent anterior resection, and Hartmann's procedure was performed in eight. Chemotherapy was given to 28 (35 per cent) of the 81 patients. In group 2, 31 patients were given a stoma and in six laparotomy only was performed. The remaining 33 patients did not undergo operation. The primary tumour was treated with radiotherapy in 15 (21 per cent) of 70 patients and eight (11 per cent) received chemotherapy.

Only 9 and 3 per cent of patients in groups 1 and 2 respectively had no symptoms from the primary tumour. In the remaining patients the most frequent symptoms were bleeding, constipation and diarrhoea. Approximately 50 per cent of the patients in groups 1 and 2 were free from concurrent disease; the other 50 per cent had at least one concurrent disease, heart

Table 1 Characteristics of patients with surgically incurable rectal adenocarcinoma diagnosed in 1973–1992

	Group 1 ($n = 81$)	Group 2 ($n = 70$)
Sex ratio (M:F)	42:39	36:34
Mean (range) age (years)	68 (42–91)	73 (50–94)
Tumour site		
Distant*	48	33
Local†	11	10
Abdominal‡	4	5
Distant and local	10	9
Distant and abdominal	8	10
Abdominal and local	0	1
Distant and abdominal and local	0	2

*Liver, lung, extra-abdominal lymph nodes, skeleton and brain; †lateral pelvic wall, sacrum, urinary bladder, vagina, uterus and prostate; ‡metastatic growth confined to peritoneal surfaces or para-aortic lymph nodes

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Paper accepted 16 November 1995

disease and diabetes mellitus being the most common. Postoperative mortality was defined as in-hospital death. Major surgical complications like ileus and anastomotic dehiscence necessitating further operation were recorded but not minor complications such as wound, respiratory and urinary tract infections.

Diagnosis of metastases

The diagnosis of metastasis was made before operation in 25 of 81 patients in group 1 and in 15 of 37 in group 2. Preoperative diagnosis was based on clinical examination, chest radiography, liver scintigraphy and, after 1978, ultrasonography and computed tomography also. The diagnosis of metastatic disease was verified histopathologically in 37 of 81 patients in group 1 and 27 of 70 in group 2.

Location of metastases

The sites of metastasis in patients in groups 1 and 2 are shown in *Table 1.*

Statistical methods

Differences in proportions were evaluated with the χ^2 test and numerical differences with Student's t test. The influence of categorical and continuous clinical variables on survival in univariate analysis was evaluated by the log rank test and Cox's proportional hazards model respectively. The latter method was also used to assess the influence of a variable on survival while simultaneously adjusting for the effects of other variables. $P < 0{\cdot}05$ was considered statistically significant.

Results

Clinical course: group 1

In group 1, the postoperative mortality rate was eight (10 per cent) of 81 patients compared with 15 (3 per cent) of 444 in group 3 ($P = 0{\cdot}02$). Nine (12 per cent) of the 73 surviving patients were discharged to other institutions compared with 21 (5 per cent) of 429 in group 3 ($P = 0{\cdot}04$). The mean hospital stay in group 1 was 21 (range 6–100) days and in group 3 24 (range 5–309) days ($P = 0{\cdot}63$).

The total number of patients in group 1 in whom ileus and anastomotic dehiscence necessitated a second surgical intervention was 14 (17 per cent) and five (14 per cent) respectively, compared with 37 (8 per cent) ($P = 0{\cdot}02$) and 15 (7 per cent) ($P = 0{\cdot}30$) respectively in group 3. The mean operating time in group 1 was 2·9 (range 1·2–5·5) h. The mean recorded peroperative blood loss was 1490 (range 250–8070) ml and the mean amount of blood transfused 1380 (range 0–12 400) ml. Median survival in group 1 was 7·5 (range 0·3–76) months.

Clinical course: group 2

In group 2, the in-hospital mortality rate was 23 (33 per cent) of 70 patients; for those who underwent surgery it was eight (22 per cent) of 37 and for those with no surgical intervention it was 15 (45 per cent) of 33. Thirty-nine of the 47 surviving patients in this group were discharged home and eight patients were sent to an institution. The mean hospital stay for patients who received a stoma was 21 (range 1–67) days, for those who underwent laparotomy 20 (range 7–43) days, and for those who did not undergo surgery 14 (range 1–45) days. The mean operating time in the 37 operated patients was 1·3 (range 0·03–2·2) h. The mean peroperative blood loss was 232 (range 0–2000) ml and the mean amount of blood transfused was 259 (range 0–2800) ml. The median survival in patients who received either a stoma only or underwent laparotomy only was 3·5 (range 0·03–19) months compared with 1·9 (range 0–46) months in those who did not undergo any form of surgery.

Two of the 39 patients without a primary stoma developed late intestinal obstruction necessitating a colostomy. Intestinal perforation in one patient also required a colostomy. One patient received laser treatment and one diathermy for bleeding and anaemia. Active surgery was thus necessary in five (7 per cent) of 70 patients because of late local symptoms. Of 15 patients with an irradiated primary tumour, two required operative intervention compared with three of 55 with unirradiated tumours.

Natural history of unresected primary tumours in group 4

A colostomy for late intestinal obstruction was performed in eight of 42 patients. Active treatment for bleeding consisted of electrocoagulation in two patients. Active surgical measures thus became necessary in ten patients in total.

Prognostic factors

Bilateral hepatic, lymph node and peritoneal metastases correlated with poor survival in univariate analysis, as did abdominal metastases (*Table 2*). Abnormal liver function test results also correlated with a short survival time in univariate analysis (*Table 3*). Liver function tests were therefore included together with metastatic sites, sex and age in a multivariate analysis for influence on survival. In this analysis, peritoneal and lymph node metastases indicated a poor prognosis in group 1 ($P < 0{\cdot}01$ and $P < 0{\cdot}02$ respectively). In a further analysis, the specific metastatic sites were replaced with abdominal metastases (para-aortic lymph nodes and/or peritoneal or local growth) *versus* distant metastases (all other sites). In this analysis, abdominal metastases ($P < 0{\cdot}01$) and increased serum alkaline phosphatase concentration ($P = 0{\cdot}03$) predicted a poor prognosis.

In a similar multivariate analysis of group 2, metastases at peritoneal and other sites (skeleton, skin and brain) predicted a short survival time ($P = 0{\cdot}02$ and $P = 0{\cdot}04$ respectively). In the model analysing abdominal *versus* distant metastases, only abdominal metastases showed a poor prognosis ($P = 0{\cdot}03$).

In the multivariate analysis of groups 1 and 2 together, the following variables predicted a short survival time: lymph node metastases ($P < 0{\cdot}001$), peritoneal metastases ($P < 0{\cdot}001$), and raised serum levels of alkaline phosphatase ($P = 0{\cdot}004$), aspartate aminotransferase (ASAT) ($P = 0{\cdot}02$) and bilirubin ($P = 0{\cdot}03$). In a final multivariate analysis with metastatic site expressed as abdominal tumour growth or not, abdominal metastases ($P < 0{\cdot}001$) and increased serum levels of alkaline phosphatase ($P = 0{\cdot}003$), bilirubin ($P = 0{\cdot}01$) and ASAT ($P = 0{\cdot}04$) correlated with a short survival.

Time trends

To determine the possible impact of time-related changes in treatment approaches on survival, the study was divided into two time periods: 1973–1982 and 1983–1992. Of the 151 patients, 31 (46 per cent) of 67 treated during the first

10-year period had the primary tumour resected. During the second period this proportion was 50 (60 per cent) of 84. Among the 486 patients without metastases the primary tumour resection rate was 218 (89 per cent) of 245 during the first period and 226 (94 per cent) of 241 in the later part of the study. The increase in resection rate was not accompanied by improved survival in patients with metastases (*Fig. 1*), but survival tended to be longer in those without metastases (*Fig. 2*). In the latter group, the projected 5-year survival rate increased from 42 to 54 per cent ($P = 0{\cdot}06$).

Discussion

Few studies have evaluated the outcome after palliative resection of rectal adenocarcinoma in population-based series[5–7]. By using population-based material, selection bias is avoided. Palliative resection of the primary tumour was undertaken in 54 per cent of the patients. Median survival was 7·5 months in resected patients compared with 3·5 months in those who had a laparotomy but no resection. This difference as well as the high in-hospital mortality rate in group 2 probably reflects a selection of

Table 2 Association between categorical clinical variables and survival in univariate analysis

	Group 1 (*n* = 81)			Group 2 (*n* = 70)			Groups 1 and 2 (*n* = 151)		
	n	Median survival (months)	*P**	*n*	Median survival (months)	*P**	*n*	Median survival (months)	*P**
Sex									
Male	42	9·5	0·02	36	1·9	0·04	78	4·6	0·46
Female	39	6·8		34	3·2		73	4·9	
Site of metastases									
Hepatic									
Yes	55	7·6	0·33	44	2·1	0·02	99	4·6	0·15
No	26	7·4		26	3·3		52	5·7	
Bilateral hepatic									
Yes	38	6·8	0·14	37	2·0	0·03	75	4·3	0·04
No	26	7·4		26	3·3		52	5·7	
Lung									
Yes	14	6·7	0·15	16	2·7	0·41	30	3·6	0·28
No	67	7·6		54	2·4		121	4·9	
Bilateral lung									
Yes	5	3·7	0·45	11	2·5	0·34	16	3·4	0·41
No	67	7·6		54	2·4		121	4·9	
Local									
Yes	21	7·3	0·18	22	3·4	0·05	43	5·9	0·39
No	60	7·5		48	2·3		108	4·6	
Lymph nodes									
Yes	7	3·1	0·002	8	1·6	0·11	15	2·4	0·01
No	74	7·9		62	2·7		136	5·7	
Peritoneal									
Yes	6	5·9	0·11	12	2·3	0·15	18	3·6	0·02
No	75	7·8		58	2·5		133	5·5	
Other									
Yes	2	11·4	—	5	0·7	0·09	7	2·0	0·11
No	79	7·6		65	2·7		144	4·9	
Abdominal†									
Yes	34	6·1	0·004	32	3·0	0·23	70	4·1	0·01
No	47	9·1		38	2·1		81	5·7	

†Metastatic growth confined to peritoneal surfaces, local sites or para-aortic lymph nodes. *Log rank test

Table 3 Relationship between continuous clinical variables and survival in univariate analysis

	Group 1 (*n* = 81)			Group 2 (*n* = 70)			Groups 1 and 2 (*n* = 151)		
	n	Relative hazard	*P**	*n*	Relative hazard	*P**	*n*	Relative hazard	*P**
Age	81	0·99	0·64	70	0·97	0·05	151	0·99	0·91
Laboratory values									
Haemoglobin	75	0·98	0·11	64	1·02	0·02	139	0·99	0·67
White cell count	73	1·06	0·18	62	1·14	0·002	135	1·08	0·01
Serum bilirubin	65	1·05	0·07	49	1·01	0·03	114	1·02	0·002
Serum alkaline phosphatase	66	1·20	0·001	49	1·04	0·01	115	1·07	0·001
Serum ASAT	66	2·96	0·03	50	1·86	0·001	116	2·32	0·001
Serum ALAT	66	1·65	0·36	50	2·93	0·002	116	3·17	0·001
Serum albumin	66	0·96	0·16	55	0·96	0·17	121	0·95	0·004

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase. *Cox's proportional hazards model

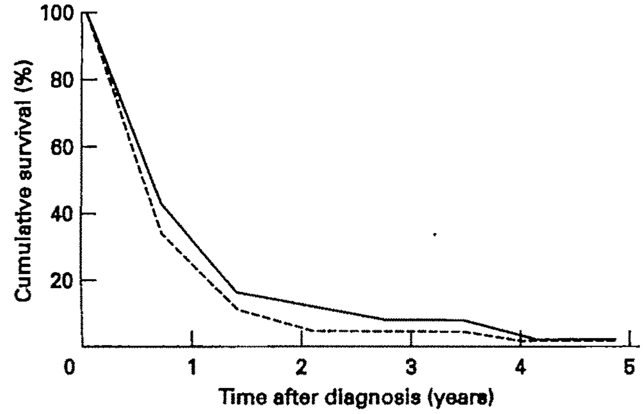

Fig. 1 Cumulative survival of 120 patients (excluding in-hospital deaths) with incurable primary rectal cancer treated in 1973–1982 ($n = 50$, ———) or 1983–1992 ($n = 70$, ----). ($P = 0{\cdot}19$, log rank test)

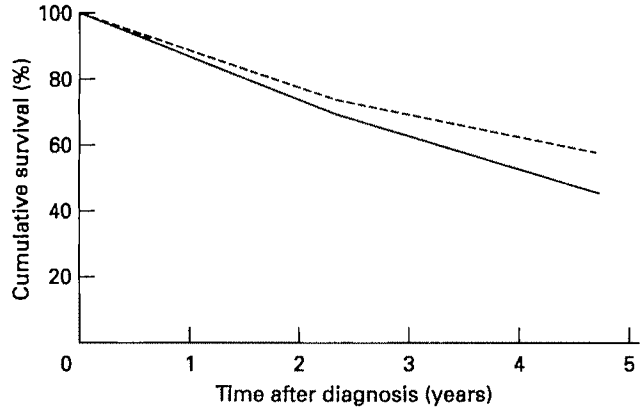

Fig. 2 Cumulative survival of 466 patients (excluding in-hospital deaths) without identifiable metastases at the time of diagnosis of the primary tumour treated in 1973–1982 ($n = 231$, ———) or 1983–1992 ($n = 235$, ----). ($P = 0{\cdot}06$, log rank test)

poor-risk patients towards less active treatment. These survival figures are clearly inferior to those of previously published hospital series[2–4,8,9], underlining the difference between population- and hospital-based series.

In view of the poor survival prospects of patients with metastatic disease at the time of diagnosis of rectal carcinoma, there is a need to select that subgroup of patients who may not benefit from surgical treatment. Two categories of poor-risk patients were identified in this study: those with abdominal tumour growth and those with extensive hepatic involvement as reflected by abnormal liver function test results or bilateral hepatic metastases. The prognostic significance of abdominal tumour growth has not been appreciated previously. The median survival in resected patients was reduced by one-third when abdominal growth was present compared with that in those without abdominal involvement. Lymph node metastases carried a particularly poor prognosis, a finding in accordance with a previous study[10]. The negative prognostic impact of peritoneal metastases and raised serum ASAT concentration has also been observed in earlier studies of patients with metastatic colorectal cancer treated with chemotherapy[11,12]. The best prognosis was seen in patients with distant metastases only and liver function test results within normal limits. Good performance patients with these characteristics are candidates for resection of the primary tumour, particularly if they have severe local symptoms.

Palliative resection has generally been recommended to control local symptoms[2–4,9]. According to the present study, about 12 (95 per cent confidence interval (c.i.) 5–19) per cent of the patients with a non-resected and non-defunctioned rectal cancer develop obstruction necessitating a colostomy. The second most common symptom demanding surgery was bleeding which required active measures in 4 (95 per cent c.i. 0–8) per cent of the patients. The total percentage of patients who developed symptoms from the primary tumour necessitating surgery was thus about 15 per cent. The need for late surgery was no lower in group 1 than in group 2, and it is therefore doubtful whether the risk of intestinal obstruction is a good reason for palliative resection. The frequency of other local symptoms such as minor bleeding, secretion, pain and incontinence could not be judged from the hospital notes. The impact of resectional *versus* non-resectional treatment on the patient's quality of life requires prospective study.

No survival advantage for pre-emptive resection of the primary tumour could be demonstrated in the time-trend analysis. Despite an increase in resection rate from 46 to 60 per cent, the survival rate was virtually identical among patients with incurable disease. In contrast, patients without metastases during the second time period tended to live longer than those treated during the first decade. Apart from the increase in resection rate from 89 to 94 per cent, the use of preoperative adjuvant radiotherapy[13] and changes in surgical technique[14] are possible explanations for this increased life expectancy. Reduced postoperative mortality may also contribute to improved survival in the curative group[15]. In fact, if in-hospital deaths were included in the calculations, improved survival was seen during the later decade in patients treated curatively ($P < 0{\cdot}05$).

In summary, resection of the primary tumour in patients with incurable rectal cancer was followed by a median survival of 7·5 months, about 4 months longer than that after laparotomy without resection. Massive liver involvement or abdominal tumour growth implied a poor prognosis. Local symptoms demanding active surgical treatment occurred in about 15 per cent of the patients with a retained primary tumour. These results suggest that selected patients with incurable rectal cancer should be managed conservatively rather than by resection of the primary tumour.

Acknowledgements

Supported by a grant from the Swedish Cancer Society project no. 3583-B94-01PAB.

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British Journal of Surgery 1996, 83, 1121–1122

Short note

Risk of extracolonic cancer in familial adenomatous polyposis

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Familial adenomatous polyposis (FAP) is characterized by the presence of more than 100 colorectal adenomatous polyps with an almost inevitable progression to cancer. At-risk individuals are screened and, if affected, prophylactic colectomy is performed. Operative options include total colectomy with ileorectal anastomosis, which affords good functional results but leaves a risk of rectal cancer[1], and restorative proctocolectomy, which should eliminate the colorectal cancer risk at the expense of an increase in morbidity[2]. Patients with FAP are also at increased risk of developing a variety of extracolorectal cancers. This study addressed the relative impact of these cancers.

Patients and methods

A total of 222 patients with FAP in whom total colectomy with ileorectal anastomosis had been performed as a primary procedure at St Mark's Hospital between 1948 and the end of 1990 were included in the study.

The cumulative probability of developing a non-colorectal cancer was calculated by the method of life-table analysis. The length of follow-up after ileorectal anastomosis was 2–45 years. Patients were included until death ($n = 33$), until diagnosis of a non-colorectal cancer ($n = 31$) or until June 1993 ($n = 158$).

Paper accepted 13 October 1995

Table 1 Details of 32 extracolonic cancers in 31 patients with familial adenomatous polyposis

Cancer	No. of patients	Median (range) age (years)
Duodenum	11	50 (34–71)
Pancreas	3	54 (46–78)
Urinary bladder	2	46 (36–55)
Testicle	2	28 (20–36)
Thyroid	1	26
Jejunum	1	53
Stomach	1	58
Brain	2	57 (56–58)
Biliary system	1	42
b.c.c.	1	57
Leukaemia	1	50
Melanoma of eye	1	55
Lymphoma	1	38
Breast	1	38
Uterus	1	52
Renal cell	1	56
Total no. of cancers	32*	51 (20–78)

*One patient had testicular cancer and renal cell carcinoma; b.c.c., basal cell carcinoma of the skin

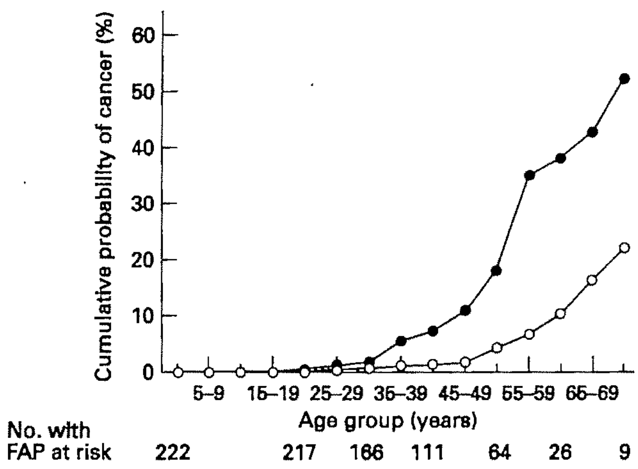

Fig. 1 Cumulative probability of developing non-colorectal cancer in a patient with familial adenomatous polyposis (FAP) (●) and of developing any cancer in the general population (○). $P < 0.0001$ (log rank test)

The cumulative probability of a patient with FAP developing a non-colorectal cancer was then compared with the cumulative risk of a member of the general population developing any cancer. These data were provided by the *Cancer Statistics Registrations* publication from the Office of Population Censuses and Surveys.

Results

Thirty-two non-colorectal cancers occurred in 31 patients (*Table 1*); one patient developed both testicular cancer and renal cell carcinoma. The cumulative probability of a patient with FAP developing a non-colorectal cancer by the age of 50 years was 11 per cent (95 per cent confidence interval (c.i.) 5·5–16·5 per cent), rising to 52 per cent (95 per cent c.i. 43–61 per cent) by the age of 75 years (*Fig. 1*). The risk of developing a cancer in the general population was much lower ($P < 0.0001$).

Discussion

It is not surprising that patients with FAP are at increased risk of developing non-colorectal cancer. The primary genetic defect in such patients is a germ-line mutation on the long arm of chromosome 5 in the *APC* gene[3]. This mutation results in a truncated APC protein product, the function of which is unknown[4]. However, within the colorectal mucosa the *APC* gene appears to control cell proliferation, an increase in cell proliferation being an early step towards carcinogenesis[5]. If the mutated gene controlled proliferation of all cells, then other organs should also be susceptible to cancer.

Preventing colorectal cancer in a patient with FAP increases the life expectancy[6]. However, the present study shows that the cumulative probability of developing a cancer outside the colon or rectum increases with age and is significantly greater than for the general population.

Almost half of these cancers are periampullary in origin, emphasizing the need for duodenal screening by regular endoscopy. Clinicians should be aware of the protean malignant manifestations of this disorder.

Acknowledgements

The authors thank the Polyposis Registrars Kay Neale and Judith Landgrebe for their help. K.P.N. was supported by the St Mark's Research Foundation.

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British Journal of Surgery 1996, 83, 1123–1127

Prediction of the risk of death by APACHE II scoring in critically ill trauma patients without head injury

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The ability of the Acute Physiology And Chronic Health Evaluation (APACHE) II scoring system to predict outcome in 199 critically ill patients with trauma but without head injury was assessed prospectively over an 8-month period. Some 178 patients (89·4 per cent) underwent operation and 50 (25·1 per cent) died, 44 after operation and six without undergoing surgery. The mean(s.d.) APACHE II score was 8·0(5·2) for survivors and 14·5(5·5) for non-survivors ($P < 0{\cdot}001$). In patients who underwent surgery the mean(s.d.) scores were 7·7(4·6) and 13·4(5·5) ($P < 0{\cdot}001$) and for those managed without operation 11·1(7·2) and 14·7(6·3) ($P = 0{\cdot}31$) in survivors and non-survivors respectively. The predicted risk of death and observed mortality rate were 5·1 and 25·1 per cent respectively for the entire group, 5 and 25 per cent for patients undergoing surgery, and 7 and 29 per cent for those not operated on. Although the APACHE II system correctly identified all survivors (specificity 100 per cent), it failed to predict death in any patient (sensitivity 0 per cent). The results suggest that this objective prognostic scoring system is not applicable to the patient with trauma who does not have concurrent head injury.

The prediction of outcome by clinical assessment of critically ill patients is prone to error for several reasons[1]. Deficiencies in the quality and quantity of data combined with a severely restricted time frame for action invite mistakes in judgement. Objective scoring systems have therefore evolved, of which Acute Physiology And Chronic Health Evaluation (APACHE) II is the most commonly used[2]. Although this system has been modified[3] to APACHE III, the system remains to be validated and the outcome prediction formula is not currently available[4]. Trauma is included in the 40 possible diagnostic categories and eight organ-system categories of APACHE II, but use of the system in patients with trauma is controversial[5–8]. Patients are grouped into those suffering head trauma alone or multiple trauma and further subdivided into those with operative or non-operative management. The risk of hospital death (R) varies with these possible combinations. Although the differences in APACHE II score to predict a 50 per cent risk of death ($R = 0{\cdot}5$) appear minimal and range from 26·5 (operative head trauma) to 32·5 (non-operative multiple trauma), an equivalent APACHE II score for these diagnostic groups results in up to a 20 per cent difference in predicted mortality rate.

Further problems exist in scoring patients with combined head and multiple system injuries or single system injury without concurrent head trauma. The recommendation is to score both as multiple system injury[5]. This difficulty has resulted in errors in outcome prediction, with a persistent underprediction of mortality in patients with a predicted risk of death of 30 per cent or more[5]. The sensitivity or ability to predict those who will die of APACHE II appears to be highest with head injury alone and lowest in patients with multiple trauma only[5]. This finding is explained by the study of Vassar *et al.*[6] in which stepwise linear regression showed that 75 per cent of the predictive power of APACHE II was determined by the Glasgow Coma Scale (GCS). Such weighting may preclude the use of APACHE II scoring in patients who fall into the diagnostic category of multiple trauma but have no associated head injury. A similar bias occurs in the Simplified Acute Physiology Score II[9] and Mortality Prediction Model[10,11], both of which are general intensive care unit (ICU) scoring systems, and also in Trauma and Injury Severity Score (TRISS)[5,12], a trauma-specific prediction method.

The surgical ICU in King Edward VIII Hospital, Durban, provides care for all forms of critically injured patients except those with major head trauma, who are treated in a separate neurosurgical unit. The value of the APACHE II scoring system was assessed in patients without head injury who required surgical ICU treatment.

Patients and methods

The study was conducted over an 8-month period (September 1992 to April 1993), during which 199 patients were admitted. Their median age was 30 (range 18–75) years and 156 patients (78·4 per cent) were male. The aetiology of injury and the mortality rates are shown in *Table 1*. Penetrating trauma accounted for 66·8 per cent of admissions (gunshot wound 45·2 per cent, stabbing 21·6 per cent). Some 178 patients (89·4 per cent) were admitted after operation and 21 (10·6 per cent) without prior surgical treatment. Of the 199 patients, 50 (25·1 per cent) died: 44 (24·7 per cent) after operation and six (29 per cent) following non-operative management.

The APACHE II score was calculated in accordance with standard recommendations (worst score for each parameter within the first 24 h of admission to the ICU) for all consecutive adult patients (aged 18 years or over). All three components of the APACHE II system (acute physiological, age, chronic health evaluation) were applied. The frequency with which the

Table 1 Aetiology of injury and mortality in 199 patients admitted to the surgical intensive care unit

	Survivors	Non-survivors
Gunshot wound	60 (67)	30 (33)
Stab wound	38 (88)	5 (12)
Motor vehicle collision	39 (75)	13 (25)
Blunt trauma	12 (86)	2 (14)
Total	149 (74·9)	50 (25·1)

Values in parentheses are percentages

Paper accepted 27 November 1995

parameters contributed to the total score is shown in *Fig. 1*. No patient was awarded points for chronic health and only 39 (19·6 per cent) for age 45 years or above. The GCS before admission was used to assign points for this physiological component for two reasons. First, postoperative analgesia and sedation made accurate assessment difficult during the first 24 h. Second, any pre-admission alteration in GCS was not as a result of direct cerebral injury and was assumed to be the lowest before supportive therapy. In this way, any bias would favour the scoring system. Twenty-eight patients (14·1 per cent) were allocated points for a reduction in GCS (hypovolaemic shock in nine, sepsis in four, cerebral ischaemia following carotid artery injury in seven, hypoxia following thoracic injury in eight).

Statistical analysis

Student's t test was used to compare differences in APACHE II score between survivors and non-survivors. Death in the surgical ICU or discharge to the surgical wards were regarded as end-points. Death after discharge from the ICU was not assessed. For each patient the risk of hospital death (R) was calculated from the formula:

$$\begin{aligned}\ln(R/1-R) = {} & -3{\cdot}517 + 0{\cdot}603 \text{ (if postoperative admission)} \\ & + \text{APACHE II score} \times 0{\cdot}146 + \text{diagnostic} \\ & \text{category weighting for either operative or non-} \\ & \text{operative multiple trauma}\end{aligned}$$

The risk of death was derived for the entire group and for groups managed with or without operation by summation of the individual risks and calculation of the mean. A 50 per cent cut-off value was used to predict death or survival. The predicted mortality rate was compared with the observed mortality rate at 10 per cent increments. Univariate analysis with an unpaired Student's t test was used to assess the association of outcome with the possible risk factors. The need for inotropic support (adrenalin infusion within the first 24 h) was compared with outcome by a χ^2 test. Multivariate analysis by multiple logistic regression with a backward elimination procedure was used to determine which factors contributed independently to survival or death. For simplicity, the ratio of arterial partial pressure of oxygen to inspired oxygen fraction (P_{aO_2}:F_{IO_2}) was substituted for P_{aO_2} or arterial–alveolar oxygen difference at all fractions of inspired oxygen. For all calculations $P<0{\cdot}05$ was used to indicate significance.

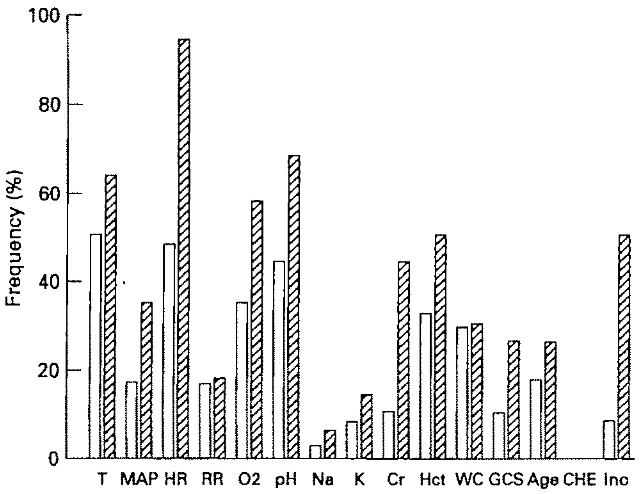

Fig. 1 Frequency of contribution of the physiological, age and chronic health (CHE) parameters to APACHE II score, and frequency of the need for inotropic support. □, Survivors; ▨, non-survivors. GCS, Glasgow Coma Scale; T, temperature; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; O2, oxygenation; Cr, creatinine; Hct, haematocrit; WC, white cell count; Ino, inotropes

Results

The APACHE II scores and risk of death for the entire group, postoperative and non-operative patients are shown in *Table 2*. The range of APACHE II scores was 0–22 for survivors and 0–27 for non-survivors. Despite highly significant differences in APACHE II score between survivors and non-survivors in the group overall and in those undergoing operation, not one patient was predicted to die. This finding is explained by the maximum APACHE II score being 27. To achieve an R value of 0·5, the APACHE II score for multiple trauma must be 31·5 for operative admissions and 32·5 for non-operative admissions. *Fig. 2* shows the observed mortality rates for 5-point increments of APACHE II score. The predicted *versus* observed outcomes in the form of a 2 × 2 matrix are shown in *Table 3* and *Fig. 3* shows the predicted *versus* observed mortality rate in 10 per cent risk increments. The sensitivity, specificity and total correct classification rate were 0, 100 and 75 per cent respectively.

Univariate analysis of the acute physiological risk factors showed that only potassium level ($t=0{\cdot}38$, 69 d.f., $P=0{\cdot}70$), haematocrit ($t=1{\cdot}79$, 188 d.f., $P=0{\cdot}07$) and GCS ($t=1{\cdot}71$, 62 d.f., $P=0{\cdot}09$) were not related to outcome. There was also no significant difference in age ($t=1{\cdot}38$, 103 d.f., $P=0{\cdot}17$). The need for inotropic

Table 2 APACHE II score, predicted risk of death and observed mortality rate in the group overall and in patients managed with and without operation

	Mean(s.d.) APACHE II score		Risk of death (%)	
	Survivors	Non-survivors	Predicted	Observed
Total ($n=199$)	8·0(5·2)	14·5(5·5)*	5·1	25·1
Postoperative ($n=178$)	7·7(4·6)	13·4(5·5)†	4·8	24·7
Non-operative	11·1(7·2)	14·7(6·3)‡	7·0	28·6

*$t=7{\cdot}49$, 189 d.f., $P<0{\cdot}001$; †$t=6{\cdot}73$, 175 d.f., $P<0{\cdot}001$; ‡$t=1{\cdot}05$, 19 d.f., $P=0{\cdot}31$

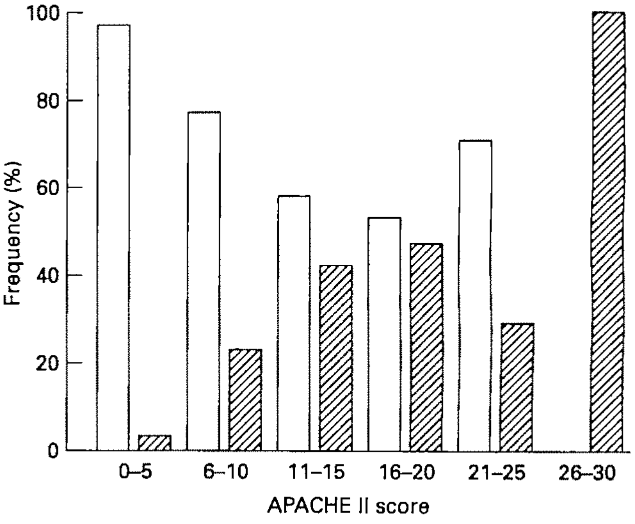

Fig. 2 Distribution of observed mortality rate in 5-point increments of APACHE II score. □, Survivors; ▨, non-survivors

Table 3 Two-by-two matrix of predicted *versus* observed mortality

	Predicted mortality	
	Non-survivors	Survivors
Observed mortality		
Non-survivors	0	50
Survivors	0	149

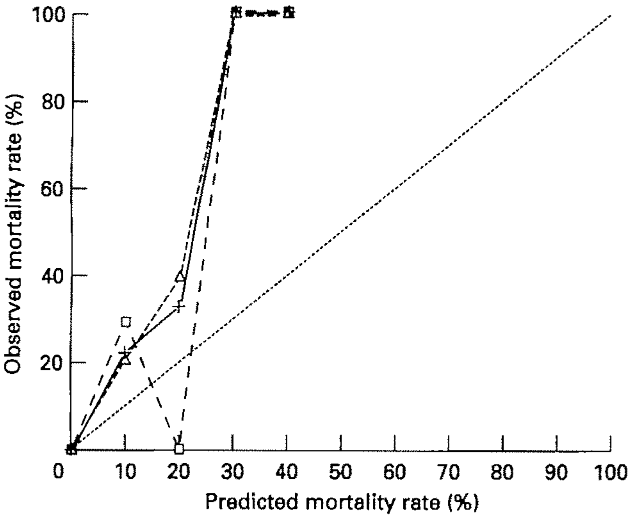

Fig. 3 Predicted *versus* observed mortality rate in 10 per cent increments of predicted mortality. +, all patients; Δ, patients after operation; □, patients managed without operation

support correlated with outcome ($P<0{\cdot}0001$). Under multivariate analysis a significant association with death was found for hypothermia, hypotension, hypoxaemia and the need for inotropic support. Applying these variables, the formula for the risk of death became:

$$\begin{aligned}\ln(R/1-R) = {} & 8{\cdot}2612 - 0{\cdot}227(\text{Temperature}) \\ & - 0{\cdot}031(\text{Mean arterial pressure}) \\ & - 0{\cdot}0047(P_{\mathrm{aO_2}}:F_{\mathrm{IO_2}}) + 2{\cdot}006\ (\text{inotropes})\end{aligned}$$

The multiplication factor for inotropes was 1 if no inotropes were used and 2 if inotropic support was required. Application of this formula to the patients under study with $R=0{\cdot}5$ as a cut-off to predict death correctly identified 92·4 per cent of survivors but only 55 per cent of non-survivors.

Discussion

Hypothetico-deductive reasoning, the most commonly used subjective strategy for medical decision-making, results in bias toward the original diagnosis, neglect of negative or non-contributory findings and over-interpretation of positive results[1]. These deficiencies have led to the development of several scoring systems in an attempt to eliminate human error from outcome prediction. Although some authors maintain that clinical judgement remains superior[7,8], most studies suggest that APACHE II predictions correlate closely with outcome in both general[13,14] and specific[15–18] critical care units.

Despite this reported success and the suggestion by the originators of APACHE II that a publishing bias exists toward negative reports[19], there appear to be genuine problems with use of the system in patients with trauma[20]. Of the total patient data base for the APACHE II study, trauma amounted to only 7·2 per cent of cases and most were due to blunt injury. The diagnostic categories are ambiguous; thus head injury combined with multiple injuries is not included in the 'head injury' category despite a heavier weighting for this injury. The impact of treatment before admission is not evaluated and there has been no detailed analysis of predictive power in the specific diagnostic groups.

The absence of head injury and of chronic health problems, together with the fact that more than 80 per cent of the present patients were under the age of 45 years, may account for the poor performance of this system. An alternative interpretation of these results would be that patient care is woefully inadequate. However, previous reports of its use, which included patients with head trauma, have consistently shown that the mean observed score for non-survivors never attained that predicted by APACHE II for a 50 per cent risk of death[5–8]. The study by Meyer *et al.*[8] shows results almost identical to those of the present analysis, suggesting that this system cannot be applied to patients with trauma. Although it may be argued that the total correct classification rate in the present study is almost 75 per cent, this mathematical concept is seriously flawed as emphasized by Ruttimann[21] because of its dependence on the sample mortality rate. In the present study all patients were predicted to live and the accuracy rate will therefore automatically be identical to the percentage survival rate. The APACHE II system was designed, however, to predict the risk of death not the probability of survival. Despite identification and application of the independent risk factors, the prediction of a fatal outcome was correct in only half of the present patients.

This study may be criticised for including only deaths occurring in the surgical ICU, whereas correct application of the APACHE II system should also include deaths after discharge from intensive therapy. Lack of a high-care step-down facility and intense pressure on the need for ventilatory support mean that patients are discharged to the standard surgical wards, where the absence of adequately trained staff and monitoring facilities may result in preventable deaths. For this reason only the surgical ICU mortality rate was assessed. The mean APACHE II score of non-survivors would probably have been even lower had hospital deaths been documented[7].

In addition to the specific problems related to its use in trauma, the APACHE II scoring system is prone to further error[4,22]. Treatment before admission to the ICU may result in over- or under-estimation of mortality rate (lead-time bias). An imprecise principal diagnosis, although uncommon in the patient with trauma, may result in the wrong diagnostic weighting (selection bias). The possibility of undiagnosed injuries should also be considered in this context. Marked physiological derangement may not be apparent within the first 24 h, but the later mortality rates are high[23]. Adverse events related to therapy rather than to the underlying disease may also contribute to an unexpected outcome[24]. A recent audit in the authors' own unit has shown this to be a relevant factor[25]. If a variable is not recorded, it is assumed to be normal in the score calculation (detection bias). The possibility of this bias increases with the number of parameters that require to be documented and their ease of collection.

The APACHE II scoring system was designed to use a categorical (cut-point) method for the weighting of variables rather than a continuous method; the latter is more applicable to progressively changing variables such as patient physiology. A similar problem arises with the use of a 50 per cent decision criterion to predict death or survival. Increasing the cut-off value of the decision criterion reduces the sensitivity of the test. Although the APACHE III system has tried to address this shortcoming by continuous prediction on a daily basis, the problem of expectation bias arises[22]. The daily prediction of the risk of death may influence treatment decisions and therefore bias outcome.

The APACHE III system[3] has been derived from more than three times the APACHE II patient data base, has included five further acute physiological variables, has modified the calculation of GCS and has altered the weighting of the physiological, age and chronic health components. The diagnostic categories have been expanded; in particular, multiple injury in association with head trauma is now classified as head trauma alone. In addition, a variable has been added to control for lead-time bias. Of the total data base of 17440 patients, however, only 8·4 per cent had conditions that were trauma related. This figure is only marginally higher than the 7·2 per cent trauma inclusion rate in the APACHE II system. Furthermore, the calculations for the risk of death are not readily available and the system awaits validation in patients with trauma.

Trauma prediction models based on data accumulated before ICU admission have been developed to assess outcome. The TRISS[12] system has become the standard method for predicting survival after injury; although not originally designed for use in the surgical ICU, it compares favourably[5] with APACHE II. The weighted version of the Revised Trauma Score[26] (RTS) and the Injury Severity Score[27] are poor predictors of outcome in patients without head injury[5]. At present, trauma-specific scoring systems appear to offer no advantage over other ICU prediction models.

Vassar *et al.*[5] have proposed a 24-h ICU point system using the GCS, $P_{aO_2}:F_{IO_2}$ ratio and 24-h fluid balance as a more accurate method of predicting outcome. Although claimed to be more sensitive than the APACHE II system, it is essentially an extended version of the RTS[26]. Their prediction model awaits validation by independent observers.

In the context of young patients without head injury or co-existent chronic disease, the present data suggest that the APACHE II system is not applicable to predicting outcome after trauma.

Acknowledgements

The authors are indebted to Miss Eleanor Gouws of the Medical Research Council Biostatistical Department for assistance with statistical analysis.

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The following text was accepted as a poster presentation at the Association of Surgeons annual meeting held in Glasgow, UK, May 1996. Because of its late acceptance it was not included in the supplement which accompanied the meeting and we are pleased to publish it now.

Shoulder immobilization following axillary node clearance

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Sixty-seven patients with carcinoma of the breast were treated by lumpectomy and level 3 axillary node clearance between August 1994 and July 1995 in this department. Immobilization of the shoulder using a collar and cuff for 10 days was evaluated in this cohort to assess whether there was a significant reduction in either axillary wound drainage or the rate of seroma formation when compared with those patients having early physiotherapy. Interviews with the patients also allowed an assessment of the acceptability of this regimen.

Axillary node clearance was performed through a vertical incision just behind the anterior axillary fold. The wound was drained with a 6-mm suction catheter, left in place for 5 days irrespective of the volume drained. Thirty-two patients were randomized to the collar and cuff while 35 were allowed free arm movement and received physiotherapy. The two groups were well matched with regard to age (mean 57, range 43–74 years), mean(s.d.) number of nodes removed (15·5(0·5)), and percentage with nodes involved by tumour (42 per cent).

Wound drainage on days 3 and 4 was less with immobilization of the shoulder, but the reduction in total hospital drainage did not reach significance. The results for seroma formation were similar (31 per cent after immobilization *versus* 43 per cent; *P* not significant). Once a seroma had developed, the clinical course was unaffected by the primary treatment, seromas resolving in a mean(s.d.) of 28(3) days. Patient interviews revealed that wearing the collar and cuff was uncomfortable and affected personal hygiene. Patients felt it delayed their return to normal activity and found it an irritating reminder to others of their recent surgery.

Shoulder immobilization after axillary node clearance does not significantly reduce seroma formation and was not acceptable to the patients. It should be withdrawn from the routine postoperative care of this group of patients.

British Journal of Surgery 1996, 83, 1128–1130

Anatomical basis of intra-arterial chemotherapy for patients with locally advanced breast cancer

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Twenty-eight patients with locally advanced breast cancer received four doses of regional chemotherapy via angiographically placed percutaneous catheters into the internal mammary artery (IMA) and lateral thoracic artery. Patent blue dye was injected to outline the relative contribution to perfusion of each of these vessels. The IMA was found to perfuse 67 (range 20–95) per cent of the breast and the lateral thoracic artery 15 (range 0–35) per cent. In 33 per cent of patients the lateral thoracic artery did not contribute to breast perfusion and a large area of the lateral aspect of the breast was perfused from a further branch of the subclavian or axillary artery. The blood supply to the breast is extremely variable and must be determined in each patient before delivering regional chemotherapy.

Despite increased public awareness, it is still not uncommon to see patients presenting with locally advanced breast cancer. Paradoxically, at presentation many of these patients have no clinical evidence of metastases, and the primary aim of treatment is to gain long-term local control. Conventionally these patients are treated with systemic chemotherapy followed by toilet mastectomy[1]. Although the response rate with these regimens varies between 60 and 80 per cent, systemic toxicity is high and local recurrence rates of up to 38 per cent have been reported[2].

Regional chemotherapy is an attractive concept which aims to deliver high doses of drug to the tumour by first-order targeting, directly perfusing the tumour-bearing organ via its arterial supply[3]. In patients with locally advanced or recurrent breast cancer, this is conventionally achieved by operative insertion of a catheter directly into the subclavian artery or into a branch of the subclavian artery, usually the thyrocervical trunk[4]. However, with this technique, the authors have found that systemic toxicity is not abolished. Furthermore, pharmacokinetic studies have shown that there is no significant difference in plasma levels following intra-arterial or intravenous administration, suggesting that intra-arterial administration by a subclavian artery catheter offers no significant regional advantage compared with intravenous administration[5].

The major blood supply to the breast arises from the perforating branches of the internal mammary artery (IMA), which penetrate the intercostal muscles near the sternum and pass through pectoralis major on their way to the medial aspect of the breast. The lateral aspect of the breast is variably supplied by branches from the second and third parts of the axillary artery, including the lateral thoracic artery[6].

A more selective approach to delivery of regional chemotherapy would be to infuse the arterial supply of the breast directly. It is possible to infuse the IMA and lateral thoracic artery by means of angiographically placed catheters[7]. This technique eliminates unwanted perfusion to the arm, shoulder and neck.

The aim of this study was to assess the variation in the distribution of the blood supply to the breast in a group of patients with locally advanced breast cancer receiving regional chemotherapy via the IMA and lateral thoracic artery.

Patients and methods

The distribution of the IMA and lateral thoracic artery was assessed in 28 patients. All patients were receiving four cycles of regional chemotherapy, mitomycin 7 mg/m^2, mitozantrone 7 mg/m^2 and methotrexate 30 mg/m^2 (MMM) at 4-weekly intervals for locally advanced breast cancer. Chemotherapy was delivered initially via the lateral thoracic artery for 2 h with a dedicated IMA catheter (Cordis UK, Brentford, UK) inserted by means of a percutaneous transfemoral Seldinger method. The catheter was then withdrawn and replaced in the IMA, and chemotherapy administered down this artery for a further 2 h.

The initial patients were part of a pharmacokinetic study and at each of the four visits they had chemotherapy delivered by a different protocol, either as an infusion or a bolus.

Before infusion of chemotherapy down each artery, 2 ml of patent blue dye (Guerbert, France) was routinely injected down the catheter to confirm its position in the origin of the vessel, and to ensure that it had not dislodged during transfer.

On the basis of this skin staining, the proportion of the breast supplied by the IMA and lateral thoracic artery was determined. A digitally analysed tracker ball system was used to calculate the percentage of breast supplied by each artery, using photographs of the patient.

Patients who achieved operability had a simple mastectomy and axillary clearance. All postmenopausal patients received tamoxifen and premenopausal patients who were found to be node positive had tamoxifen and systemic chemotherapy.

Results

The mean area of the breast supplied by the IMA was found to be 67 (range 20–95) per cent; for the lateral thoracic artery the mean was 15 (range 0–35) per cent. In 33 per cent of patients the whole breast was not supplied exclusively by the IMA and lateral thoracic artery, and subclavian angiography and patent blue staining showed that a portion of the breast was supplied by further branches of the subclavian or axillary arteries (*Fig. 1*).

Systemic toxicity was minimal, with no patient suffering greater than grade I or II toxicity. Of the 28 patients, six developed local skin toxicity; mitomycin C has since been eliminated from the regimen.

Paper accepted 27 November 1995

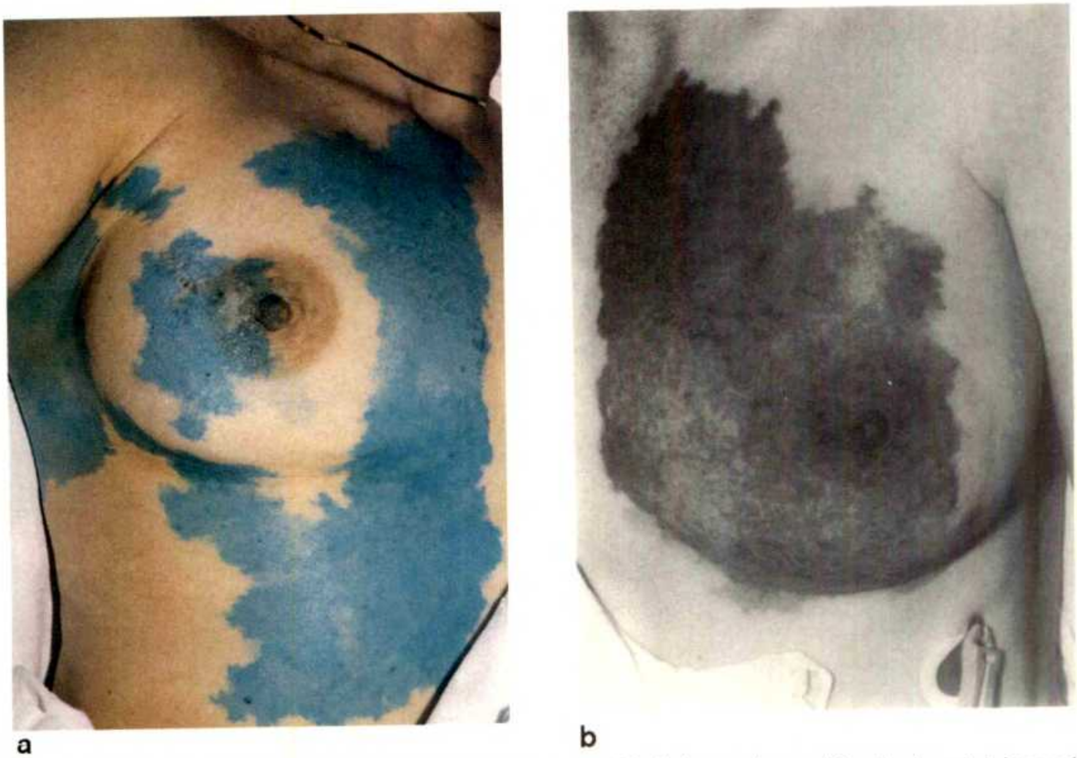

Fig. 1 Blue dye demonstrating variation in the blood supply to the breast. **a** Multiple vessels supplying the breast; **b** internal mammary artery supplying a large area of the breast following distal coil embolization

Discussion

The central aim of treatment of primary inoperable breast cancer is to establish good long-term local control. Systemic chemotherapy can achieve response rates of 60–80 per cent[2]; attempts to increase the dose–response rate by dose escalation have been frustrated by the development of unacceptable toxicity. Attention has therefore turned to the concept of targeted therapy. Most cytotoxic drugs have a steep dose–response curve. It is therefore a basic pharmacokinetic principle that increased drug exposure will increase the response rate. Widder *et al.*[8] described three levels of targeting: first-level targeting in which the cytotoxic agent is directed towards the tumour-bearing organ, in this case the breast; second-level targeting where the drug is directed towards the tumour rather than normal tissue; and third-level targeting where drug uptake by the tumour is enhanced[8]. Intra-arterial therapy achieves first- and to some extent second-level targeting.

Conventionally, regional therapy is delivered by operative insertion of a catheter directly into the subclavian artery or one of its branches, usually the thyrocervical trunk[4]. Administration by this method produces perfusion of the neck, back and trunk as well as of the breast. A tourniquet has to be applied to protect the arm, thus limiting the duration of infusion to 15 min. The authors' experience of this technique, administering MMM every 4 weeks, showed that, although the clinical response rate was encouraging, systemic toxicity was high. Furthermore, pharmacokinetic studies showed no significant regional advantage when administering chemotherapy by this method compared with intravenous administration[5].

A more selective approach and improved scheduling might, however, provide an increased regional advantage. A more selective approach can be achieved by angiographic placement of catheters directly into the IMA, so eliminating unwanted perfusion of the neck, trunk and arm. Because there is no tourniquet, perfusion times can be increased, thereby improving scheduling[9]. However, almost half of breast cancers arise in the upper outer quadrant of the breast where there is relatively more breast tissue, and one-quarter arise centrally. Breast cancer is also multifocal in 30 per cent of cases. Delivery of regional chemotherapy via the IMA alone will inadequately perfuse these tumours. A further disadvantage of this technique is that perfusion of the anterior abdominal wall (via the superior epigastric artery) and diaphragm (via the musculophrenic artery) occurs. This can produce ulcers of the anterior abdominal wall or phrenic nerve paralysis[10,11]. However, these complications can be readily prevented by coil embolization of the distal IMA beyond the last branch to the breast[12] (*Fig. 1b*).

This study has demonstrated that the blood supply to the breast shows marked variation amongst individual patients. The proportion of breast being supplied by the IMA and lateral thoracic artery varied from 20 to 95 per cent and from 0 to 35 per cent respectively. In 33 per cent of patients there was an additional arterial supply from either the subclavian or axillary artery. Therefore, to ensure that tumours are adequately perfused, it is necessary to perfuse both IMA and whichever vessel supplies the lateral aspect of the breast. If this is carried out, adequate perfusion can be obtained, perfusion times can be prolonged and unwanted perfusion of the anterior abdominal wall and diaphragm can be eliminated by distal coil embolization. This approach offers a highly selective route and method of delivery of cytotoxic drugs in patients with primary inoperable breast cancer.

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British Journal of Surgery 1996, 83, 1131–1132

Short note

Prevention of voice change in singers undergoing thyroidectomy by using a nerve stimulator to identify the external laryngeal nerve

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The external laryngeal nerve (ELN) is intimately associated with the superior thyroid vessels (*Fig. 1*) and may be stretched by a retractor or transected when these vessels are divided during thyroidectomy. Damage to the ELN causes paralysis of the cricothyroid muscle and changes to the voice that may include hoarseness, weakness, decreased range of pitch or volume and fatigue after extensive use[1]. These changes tend only to be a nuisance in most individuals but can be catastrophic in singers or professional speakers. In 1935 the career of the famous opera singer Amelita Galli-Curci ended abruptly following possible damage to the ELN sustained during thyroidectomy under local anaesthesia.

Individual ligation of the glandular branches of the superior thyroid artery can reduce the incidence of voice change following thyroidectomy[1] but even with this technique it is unusual to visualize the nerve because of its small size and variable course[2,3]. The authors describe the use of a nerve stimulator as an aid to identification and protection of the ELN in three singers who required thyroidectomy.

Patients and methods

Three women presented with solitary thyroid nodules that were increasing in size and causing cosmetic and compression symptoms. One patient was a professional singer, another semiprofessional and the third was a lifelong member of a choral society who described her amateur singing as 'her life'. Thyroidectomy was performed through a standard 'collar' incision without division of the strap muscles. The superior thyroid pole was grasped using an Allis forceps, gently drawn caudally and rotated laterally to demonstrate the cricothyroid space. A nerve stimulator (Xomed-Treace Pulsatron II, Downs Surgical, Sheffield, UK) was then used to demonstrate the ELN. Stimulation of the nerve produced obvious contractions of the ipsilateral cricothyroid muscle. Individual branches of the superior thyroid artery were tested with the nerve stimulator before ligation in order to exclude a closely associated ELN branch. Following exposure of the recurrent laryngeal nerve, total thyroid lobectomy was performed. Sutures were removed and the patients discharged on the second day after operation.

Paper accepted 15 October 1995

Results

There were no postoperative complications in these patients. On the first two days after surgery their voices sounded normal; this impression was confirmed by the patients themselves. All three returned to natural singing within 6 weeks and reported that there were no changes in the pitch or range of their voices.

Discussion

Avoidance of voice change is important in all patients having thyroidectomy but is absolutely vital in singers. The use of a nerve stimulator during thyroidectomy has previously been described[4,5] but there are no reports relating to singers. A nerve stimulator is a useful safeguard in these patients. Although the authors have not used objective measures to detect voice change, it was not necessary to do this to prove the value of the method because very minor voice alterations are easily detected by patients and our three singers have reported no changes in their vocal performances after surgery.

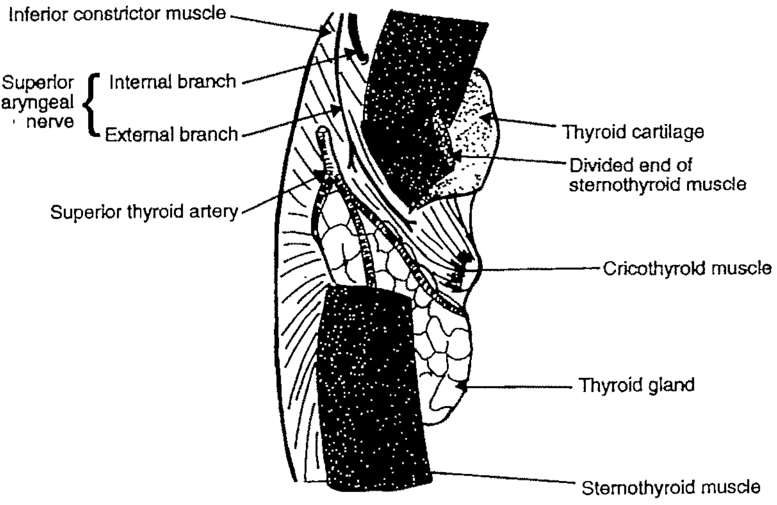

Fig. 1 Anatomy of the external laryngeal nerve

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British Journal of Surgery 1996, **83**, 1132

Case report

Bilateral recurrent phaeochromocytoma associated with a growth hormone-secreting pituitary tumour

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Multiple endocrine neoplasia (MEN), a group of neoplasia syndromes characterized by tumours of more than one endocrine gland, has been divided into three subtypes. MEN1 is characterized by neoplasia of the parathyroid glands, the anterior pituitary, the endocrine pancreas and duodenum. MEN type 2A comprises medullary carcinoma of the thyroid, phaeochromocytoma and parathyroid hyperplasia, whereas MEN2B refers to medullary carcinoma of the thyroid, phaeochromocytoma, intestinal neurogangliomatosis and a marfanoid habitus[1]. Genetically, MEN1 and MEN2 are two distinct syndromes as MEN2A and MEN2B are related to mutations of the RET proto-oncogene[2] and MEN1 to mutations in a putative tumour suppressor gene at chromosome 11q13. Except for parathyroid disease, the association of the overlapping features of both types is extremely rare. Here, a case of recurrent bilateral phaeochromocytoma associated with a growth hormone (GH)-producing pituitary tumour is reported.

Case report

A 41-year-old man was admitted for investigation of hypertension (blood pressure 180/110 mmHg), flushing and sweating. He had obvious acromegalic features and a kyphoscoliosis. At the age of 20 years he had undergone removal of right adrenal and left para-aortic phaeochromocytomas. The same year, he had a transphenoidal hypophysectomy to remove a GH-secreting pituitary tumour. Four years later a left phaeochromocytoma was removed.

During the current admission, a meta iodo-biguanide (MIBG) scan demonstrated bilateral tumours in the region of the renal hilum; a 6·5 × 3·5 × 3·0-cm tumour was removed from the right and a 4·0 × 2·0 × 2·0-cm tumour from the left. Histological examination confirmed phaeochromocytoma with capsular and vascular invasion, but there was no evidence of mitotic figures or lymph node involvement. The patient recovered. During each of his previous and current admissions, he was screened for other endocrinopathies, including medullary carcinoma of the thyroid, hyperparathyroidism, and endocrine pancreatic tumours, but to date all have been negative. However, he refused permission for family screening for MEN.

The RET proto-oncogene was screened for germ line mutation. All exons were screened by single-strand conformation polymorphisms (SSCP), and in addition, exons 10, 11 and 16, which are known to harbour the MEN2-related mutations, were investigated by direct sequencing[2,3]. No aberrant bands were detected in any exon with SSCP, while direct sequencing did not detect any mutation.

Paper accepted 11 October 1995

Discussion

To date, we are not aware of any report of the association of bilateral phaeochromocytoma and GH-secreting tumour. The occurrence of both tumours in this patient at a relatively young age and the bilateral nature of the phaeochromocytoma point towards a common germ line genetic trigger rather than a pure coincidence for two sporadic endocrine tumours (approximately $1:10^{12}$). As no germ line mutation in the RET proto-oncogene was found, there was no indication for prophylactic thyroidectomy or other invasive measures[4,5]. However, the patient will require close follow-up and, when the MEN1 gene is identified, it will be of interest to perform its mutation analysis.

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British Journal of Surgery 1996, 83, 1133–1135

Coagulation and fibrinolytic responses of human peritoneal fluid and plasma to bacterial peritonitis

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Significantly higher ($P < 0.05$) thrombin–antithrombin III complex levels were found in the abdominal exudate of patients with peritonitis (median 5500 ng/ml) than in that of controls (median 89 ng/ml). In patients, peritoneal fluid concentrations of tissue and urokinase-type plasminogen activator were increased by factors of 65 and 10 respectively ($P < 0.05$). The concentration of plasminogen activator inhibitor (PAI) 1 was increased by a factor of about 800 (median 395 *versus* 0·5 ng/ml, $P < 0.05$). Despite markedly raised concentrations of PAI, peritoneal fluid displayed fibrinolytic activity as demonstrated by significantly increased ($P < 0.05$) concentrations of plasmin–α_2-antiplasmin complex (median 10 952 *versus* 57 ng/ml) and fibrin degradation products (median 40 360 *versus* 126 ng/ml). There was no correlation between plasma and peritoneal fluid concentrations. Intra-abdominal coagulation and fibrinolysis are stimulated in the abdominal cavity of patients with bacterial peritonitis.

In bacterial peritonitis, fibrin is formed in the peritoneal cavity as a result of activation of the intra-abdominal coagulation cascade. Intraperitoneal fibrin plays a key role in the local host response to bacterial invasion, and prevents early bacteraemia and sepsis by entrapment of bacteria[1]. The role of fibrin is only temporary and fibrin must be degraded for normal tissue function to resume. When intra-abdominal fibrin persists, it acts as a nidus for infection, resulting in an intra-abdominal abscess[2]. In patients with bacterial peritonitis, intra-abdominal abscesses are associated with marked morbidity and mortality[3,4].

For the degradation of intra-abdominal fibrin, stimulation of the intraperitoneal fibrinolytic system is required. However, fibrinolytic activity is reduced during bacterial peritonitis, as has been demonstrated in several experimental studies[5–7]. Diminished release of tissue plasminogen activator (tPA) and increased release of plasminogen activator inhibitor (PAI) from peritoneal tissue have been considered to be important reasons for the reduced fibrinolysis[7]. Recently, the authors have demonstrated an increase in both tPA and PAI activity in the abdominal exudate of rats with faecal peritonitis, but this did not correlate with the extent of peritoneal damage[6]. In patients with peritonitis, research has thus far been confined to the fibrinolytic properties of the peritoneum[8]. The aim of the present study was to assess coagulation and fibrinolytic activity in the abdominal exudate and plasma of patients with bacterial peritonitis.

Patients and methods

Study design

Ethical approval was obtained from the hospital ethics committee. Twenty-five patients who underwent emergency laparotomy for peritonitis were studied. Peritonitis was due to perforated appendicitis in ten patients, duodenal perforation in five, perforated diverticulitis in five, small bowel perforation in two, toxic megacolon with perforation in two, and infected ascites due to pancreatic necrosis in one. Abdominal cultures revealed bacterial growth in all patients. There were 16 male and nine female patients of mean age 48 (range 11–90) years.

Seven patients undergoing elective cholecystectomy for gallstone disease served as controls (three men and four women, mean age 50 (range 12–75) years). Bacterial cultures of the peritoneal fluid were negative in all control patients. After incision and meticulous haemostasis, 10 ml of peritoneal fluid were aspirated from the abdominal cavity of all patients with peritonitis. In patients undergoing cholecystectomy, the amount of fluid aspirated varied between 0·5 and 2 ml, and was diluted with normal saline to a total amount of 10 ml.

Venous blood (10 ml) was drawn simultaneously with peritoneal fluid aspiration. Peritoneal fluid and blood were collected in a citrate tube (1:10) and a Stabilyte (Biopool, Umea, Sweden) tube (1:10) respectively, and placed in melting ice[9]. Within 30 min the samples were centrifuged at 4°C and the supernatants stored at − 80°C until assays were performed.

Activation of coagulation was assessed by measuring the thrombin–antithrombin III (TAT) complex, as thrombin generation is the final step in the coagulation cascade before fibrin formation.

To analyse fibrinolysis, tPA, urokinase-type plasminogen activator (uPA), PAI-1, plasmin–α_2-antiplasmin (PAP) complex and fibrin degradation products were measured.

Assays

The concentration of TAT complex was measured by enzyme-linked immunosorbent assay (ELISA) (Enzygnost TAT; Behringwerke, Marburg, Germany).

The level of tPA antigen was measured by ELISA (Asserachrom tPA; Boehringer, Mannheim, Germany). The assay measures both free and complexed (with PAI-1) human tPA and is calibrated against the international standard for tPA. tPA activity was measured by Coaset-tPA assay (Kabi Diagnostica, Molndal, Sweden), as described by Nilsson *et al.*[10].

PAI-1 antigen levels were measured by ELISA (Biopool, Umea, Sweden). The assay measures free, latent as well as complexed (with tPA or uPA) human PAI-1. PAI activity was measured by Berichrom-PAI assay (Behringwerke), as described by Stief *et al.*[11].

The level of uPA antigen in plasma and peritoneal fluid was measured by ELISA, according to the method of Binnema *et al.*[12]. Concentrations were expressed as a percentage of the uPA concentration in normal pooled plasma of healthy volunteers.

PAP complex was measured by ELISA (EIA APP micro; Behringwerke). Fibrin degradation products were measured by ELISA (Fibrinostika FbDP; Organon Technika, Turnhout, Belgium).

The validity of the assays was not affected by the dilution of peritoneal fluid in control patients.

Paper accepted 27 November 1995

Table 1 Parameters of coagulation and fibrinolysis in the peritoneal fluid of patients with peritonitis and controls

Peritoneal fluid	Peritonitis (*n* = 25)	Controls* (*n* = 7)
tPA antigen (ng/ml)	66·1 (37·5–180·0)	1·1 (0·5–1·8)†
tPA activity (units/ml)	6·5 (3·7–11·9)	<0·25 (<0·25–0·3)†
PAI antigen (ng/ml)	395 (147–588)	0·5 (<0·5–1·3)†
PAI activity (units/ml)	14·3 (7·4–22·2)	<0·3 (<0·3 to <0·3)†
uPA antigen (%)	740 (168–2000)	78 (14–168)†
TAT complex (ng/ml)	5500 (2976–9094)	89 (30–198)†
PAP complex (ng/ml)	10952 (4834–15469)	57 (17–123)†
Fibrin degradation products (ng/ml)	40360 (6475–200000)	126 (31–463)†

Values are median (95 per cent confidence interval). *Results corrected for dilution at sampling. tPA, Tissue-type plasminogen activator; PAI, plasminogen activator inhibitor; uPA, urokinase-type plasminogen activator; TAT, thrombin–antithrombin III; PAP, plasmin–α_2-antiplasmin. †$P<0{\cdot}05$ (patients with peritonitis *versus* controls, Mann–Whitney *U* test)

Table 2 Parameters of coagulation and fibrinolysis in the plasma of patients with peritonitis and controls

Plasma	Peritonitis (*n* = 25)	Controls (*n* = 7)
tPA antigen (ng/ml)	7·9 (4·9–12·6)	6·4 (3·4–10·3)
tPA activity (units/ml)	2·3 (1·7–3·3)	1·3 (0·9–2·4)
PAI antigen (ng/ml)	15·0 (10·2–22·3)	13·8 (5·9–39·9)
PAI activity (units/ml)	1·7 (0·9–2·9)	1·4 (0·8–2·3)
uPA antigen (%)	204 (138–272)	120 (96–172)*
TAT complex (ng/ml)	5·2 (3·3–16·5)	2·6 (1·4–5·5)
PAP complex (ng/ml)	709 (450–917)	381 (290–567)
Fibrin degradation products (ng/ml)	1201 (559–2867)	350 (193–594)*

Values are median (95 per cent confidence interval). tPA, Tissue-type plasminogen activator; PAI, plasminogen activator inhibitor; uPA, urokinase-type plasminogen activator; TAT, thrombin–antithrombin III; PAP, plasmin–α_2-antiplasmin. *$P<0{\cdot}05$ (patients with peritonitis *versus* controls, Mann–Whitney *U* test)

Statistical analysis

Data are expressed as median values and 95 per cent confidence intervals. The Mann–Whitney *U* test was used for analysis of differences between groups. Correlations between plasma and peritoneal fluid values were analysed by Spearman's rank test. $P<0{\cdot}05$ was considered significant.

Results

Activation of coagulation in the abdominal exudate of patients with peritonitis was demonstrated by significantly higher TAT complex concentrations, compared with controls (*Table 1*). Stimulation of the fibrinolytic system in the peritoneal fluid of patients with peritonitis was demonstrated by significantly raised levels of tPA, uPA, PAP complex and fibrin degradation products, compared with those found in the peritoneal fluid of controls (*Table 1*). Median peritoneal fluid concentrations of tPA and uPA in patients with peritonitis were about 65- and tenfold respectively higher than values in controls. PAI-1 antigen showed an 800-fold increase. Hence, concentrations of PAP complex and fibrin degradation products in the peritoneal fluid of patients with peritonitis were significantly raised in comparison with those in controls.

By contrast, plasma concentrations of TAT and PAP complex, and tPA and PAI-1 antigen and activity, were comparable in patients with and without peritonitis. Only plasma concentrations of uPA antigen and fibrin degradation products in patients with peritonitis were higher than those in control patients (*Table 2*).

Neither in those with peritonitis nor in control patients did the level of any coagulation or fibrinolytic factor measured in the plasma correlate with that observed in the peritoneal fluid.

Discussion

This study demonstrates that, in the abdominal cavity of patients with bacterial peritonitis, both the coagulation cascade and the fibrinolytic system are stimulated. The resultant deposition of fibrin probably reflects a relative deficit of fibrinolytic activity, resulting from strongly enhanced inhibition of plasminogen activators.

The markedly raised concentration of TAT complex in the peritoneal fluid of all patients with peritonitis demonstrates intraperitoneal stimulation of coagulation. The coagulation cascade may be triggered by expression of tissue factor (procoagulant activity) on injured mesothelial and endothelial cells in the peritoneum[13–15] and on peritoneal macrophages, which express tissue factor following stimulation with, for example, endotoxin and tumour necrosis factor (TNF)[15,16]. The relative contribution of separate cell types to intra-abdominal coagulation has not yet been clarified. It seems that activation of coagulation was confined to the abdominal cavity, as the plasma TAT complex concentration in most patients with peritonitis was not raised. In a few patients with sepsis, high plasma levels of TAT complex were found, which is in concordance with earlier reports on the relationship between sepsis and systemic hypercoagulability[17,18].

These data show increased levels of fibrinolytic activators following peritonitis. This finding is in agreement with that of Dörr *et al.*[19], who reported increased fibrinolytic activity and fibrin degradation in the peritoneal fluid of women with pelvic inflammatory disease. Increased tPA antigen levels in the peritoneal fluid, associated with normal plasma levels of tPA antigen in patients with bacterial peritonitis, suggest local production of tPA. In particular, mesothelial cells and submesothelial endothelium might be responsible for the production of tPA[20,21]. The increased tPA concentrations found in the present study might be explained by prompt release from a preformed storage pool within these cells. Several 'stress factors' and inflammatory mediators, stimulated by bacterial infection, may induce such a release of tPA *in vivo*[22]. However, these findings are not supported by *in vitro* experiments in which inflammatory stimuli, such as TNF and interleukin 1, inhibited tPA release by cultured mesothelial and endothelial cells[21,23]. Alternatively, increased levels of tPA might be caused by leakage from mesothelial cells, which are damaged during peritoneal infection.

PAI-1 forms a 'one to one' inactive complex with both tPA and uPA. Because the increase in PAI-1 concentration in the peritoneal fluid of patients with peritonitis was much higher than that of tPA and uPA, complete inhibition of fibrinolytic activity in the abdominal cavity might be expected. However, plasmin activity has occurred, as shown by the raised levels of PAP complex and fibrin degradation products. As plasminogen activation, mediated by tPA, is significantly enhanced in the presence of fibrin, tPA may display fibrinolytic effects even in the presence of a high PAI-1 level[24,25].

The rise of uPA in the peritoneal fluid of patients with peritonitis is probably not linked to mesothelium, but to endothelium, as uPA has not been demonstrated in mesothelial, but in endothelial, cells of biopsies of inflamed appendices and in *in vitro* cultures, following stimulation with inflammatory cytokines[26,27]. The more pronounced increase in uPA levels in peritoneal fluid, compared with that in plasma, might be explained by the direction of secreting uPA by endothelial cells, which is mainly abluminal[27]. Except for a relatively small increase in uPA and fibrin degradation products concentrations, plasma levels were not raised in patients with peritonitis. Based on the findings of predominantly normal plasma levels, as well as the absence of correlation between plasma and peritoneal fluid levels, the authors hypothesize that the abdominal cavity with its surrounding peritoneum acts as a separate compartment. The coagulation and fibrinolytic responses to bacterial peritonitis in this compartment, and the systemic effects, depend on many factors, of which individual contributions are difficult to assess. It seems that the increase in fibrinolytic activity during peritonitis is limited by high PAI-1 levels, and does not meet the overwhelming demand to overcome fibrin production.

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British Journal of Surgery 1996, 83, 1136–1137

Short note

Effect of injection of triamcinolone on type 1 procollagen and fibronectin in scar tissue

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Hypertrophic and keloid scar formation are common following median sternotomy. The authors have previously identified a biochemical marker in scars, namely type 1 procollagen peptide, which correlates with the macroscopic appearance of sternotomy scars[1]. Antibodies to type 1 procollagen recognize the portion of the amino- or carboxyl-terminal domains of type 1 procollagen molecule which are proteolytically removed during collagen secretion. Thus, antibody staining identifies cells actively synthesizing type 1 collagen and hence contributing to scar formation.

Paper accepted 27 October 1995

The present study sought to determine whether measurement of type 1 procollagen peptide could be used in the evaluation of methods of scar reduction. This study aimed to discover whether injection of corticosteroids into a wound 6 weeks after operation would reduce the abundance of type 1 procollagen staining.

Patients and methods

Twenty patients were recruited 6–8 weeks after undergoing median sternotomy for cardiac surgery. The standard surgical technique employed was incision of skin by scalpel and of deep layers by diathermy with skin closure using subcuticular 2/0 polyglycolic acid sutures. Patients were given flucloxacillin for 5 days and either gentamicin or cefuroxime for 48 h over the operative period according to renal function. Two randomly allocated 2·5 cm regions in the lower 10 cm of the scar were injected with 0·1 ml drug solution or 0·1 ml saline. Drug solutions were either triamcinolone acetonide (Lederle Laboratories, Gosport, UK) 10 mg/ml (11 patients) or 5 mg/ml (nine patients).

One week after injection a 3-mm punch biopsy was taken from both drug and placebo injection sites. Immunochemical examination was performed with standard methods[1] on formalin-fixed paraffin sections of the biopsies using antibodies against type 1 procollagen (Chemicon International, Temecula, California, USA), transforming growth factor (TGF) β (R & D Systems, Abingdon, UK), fibronectin (Sigma Chemicals, Poole, UK) and α smooth muscle actin (Dako, High Wycombe, UK). All the secondary antibodies and the ABC kit were obtained

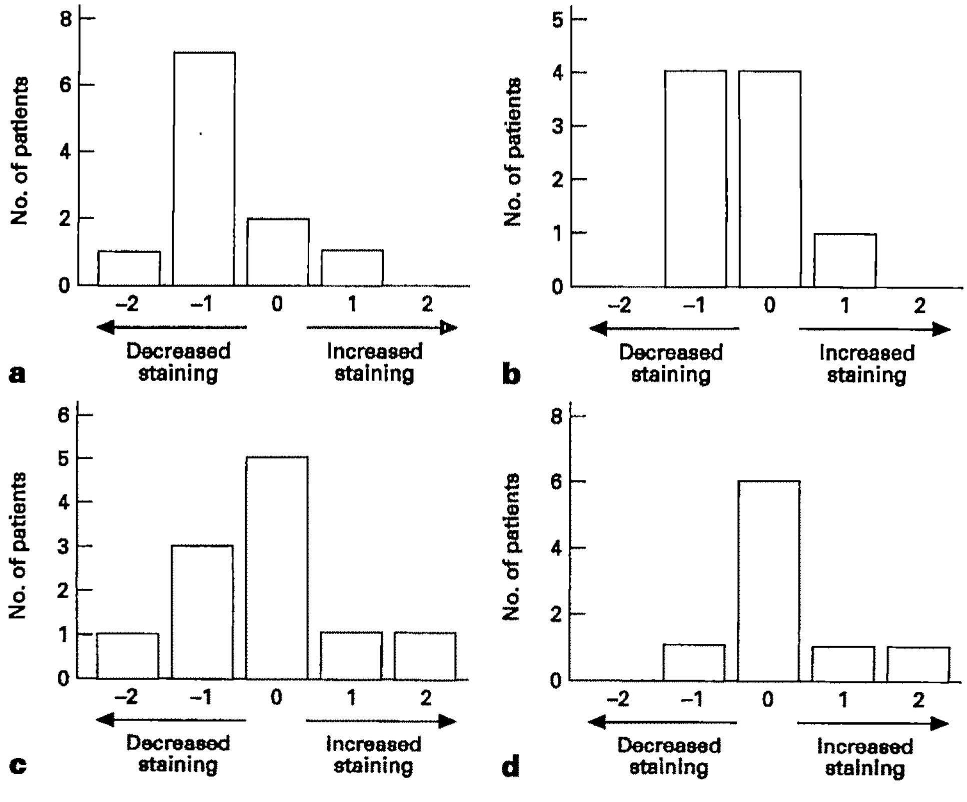

Fig. 1 Number of patients demonstrating a change in the grade of type 1 procollagen immunostaining after **a** high-dose and **b** low-dose triamcinolone, and in the grade of fibronectin staining after **c** high-dose and **d** low-dose triamcinolone, compared with saline. A high dose (**a** and **c**) consisted of a 0·1 ml injection of a 10 mg/ml triamcinolone solution and a low dose (**b** and **d**) 0·1 ml of a 5 mg/ml solution

from Dako. Grading of sections was performed by a pathologist blind to the code, using a scale of 0, +/−, +, + +, + + +. Biopsies from drug- and placebo-treated regions of the same patient were compared and the difference in the staining grade recorded. *In situ* hybridization for procollagen messenger RNA (mRNA) was performed as described previously[2].

The study was approved by the local ethics committee. Statistical analysis was carried out using the Wilcoxon matched-pairs signed rank test.

Results

By means of haematoxylin and eosin staining, scars were seen to comprise focal aggregates of chronic inflammatory cells in scar tissue. Immunohistochemical staining for type 1 procollagen identified collagen-producing fibroblasts in both cellular matrix and perivascular areas. *In situ* hybridization confirmed the presence of type 1 collagen mRNA in these sections from post-sternotomy scars. There was binding of the probe to cells within the matrix, which was absent when sections were treated with ribonuclease before hybridization.

Local injection of the higher dose (10 mg/ml) of triamcinolone resulted in a significant reduction in immunostaining for type 1 procollagen compared with placebo (*Fig. 1*). This reduction was not observed with the lower dose of triamcinolone (5 mg/ml). There was little change in fibronectin staining following administration of triamcinolone. Staining using antibodies against TGF-β and α smooth muscle actin was weak in all sections and did not alter with therapy. No macroscopic differences in the area of scar treated by either triamcinolone or placebo were observed.

Discussion

The authors' previous study[1] suggested that measurement of type 1 procollagen in a wound might serve as a biochemical marker for the intensity of the scarring process and that this might correlate with macroscopic appearance. In the present study, local injection of a relatively high dose of corticosteroid altered the intensity of type 1 procollagen staining in the scar and, by inference, might reduce the intensity of the subsequent scarring process. The observation that corticosteroids reduce type 1 collagen production agrees with other *in vitro* studies[3], although fibroblasts from hypertrophic or keloid scars may be relatively refractory to corticosteroids[4]. Local injection of corticosteroids has been used to prevent hypertrophic scarring[5], although there is concern that this approach may impair wound healing.

The use of a biochemical marker of new collagen production in short-term studies on the intensity of the scarring process may offer a way to develop and assess new therapies to prevent the clinical problem of disfiguring scars.

Acknowledgements

This study was supported by the Medical Research Council and British Lung Foundation.

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British Journal of Surgery 1996, 83, 1138–1143

Food intake after gastrectomy for gastric carcinoma: the role of a gastric reservoir

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Patients with carcinoma of the stomach who underwent curative resection were randomized to total gastrectomy ($n=49$), total gastrectomy and an S-shaped gastric substitute ($n=28$) or subtotal gastrectomy ($n=12$); all had a Roux-en-Y reconstruction. The gastric substitute and gastric remnant allowed a volume of 400–500 ml to be installed without increments in basal pressures. The corresponding volume in the Roux limb was 100 ml. Energy intake was approximately 120 kJ/kg preoperative weight per day 3 months after operation, and then remained constant. Patients who had subtotal gastrectomy ate less (91·7 kJ/kg preoperative weight) 3 months after operation, but thereafter increased their intake. Patients allocated to have a gastric pouch or subtotal gastrectomy complained more frequently of adverse postprandial symptoms ($P<0·03$) as a major cause of reduced calorie intake. The construction of a gastric reservoir did not improve nutritional adaptation after surgery for gastric carcinoma.

The role of total gastrectomy in the surgical treatment of gastric carcinoma remains a controversial issue. Recent controlled clinical trials have shown that mortality and morbidity after total gastrectomy reach the same levels as after more limited surgical procedures[1–4]. On the other hand, the impact of the experience and skill of the operating surgeon on the postoperative complication rate has to be considered[5].

Different reconstructive procedures after total gastrectomy have been described, although the Roux-en-Y oesophagojejunostomy is preferred because it prevents alkaline reflux oesophagitis[1–6]. Total gastrectomy often results in weight loss, malabsorption, disturbed eating habits and impaired dietary intake[7–9], and postprandial symptoms are also prevalent. To allow larger meals to be consumed after total gastrectomy, construction of enteric reservoirs has been advocated[10]. Although favourable reports have been presented, few prospective controlled studies have been performed to evaluate these reservoirs. The aim of the present study was to examine the reservoir function of an S-shaped jejunal gastric pouch and to evaluate the effect of a gastric remnant of equal size on the amount of food eaten during each meal.

Patients and methods

Consecutive patients with gastric cancer, suitable for resection with curative intent, were included in the study. The decision to include was finally made at the time of exploration, when the tumour was macroscopically judged to be resectable 'for cure'. Patients were randomized to have subtotal gastrectomy, leaving about 25 per cent of the stomach intact or total gastrectomy with a Roux-en-Y oesophagojejunostomy if the carcinoma was located in the distal third of the stomach. However, in those with the carcinoma located in the middle or proximal part of the stomach, the randomization was between a straight Roux-en-Y oesophagojejunostomy or a gastric substitute after total gastrectomy. Forty-nine patients were allocated to total gastrectomy, 28 had a gastric substitute and 12 subtotal gastrectomy. Clinical data and tumour status are given in *Tables 1* and 2.

Table 1 Characteristics of patients with carcinoma of the stomach treated by total gastrectomy with Roux-en-Y oesophagojejunostomy or gastric substitute, or by subtotal gastrectomy

	Roux-en-Y ($n=49$)	Gastric substitute ($n=28$)	Subtotal gastrectomy ($n=12$)
Mean (range) age (years)	67 (41–85)	64 (36–82)	72 (63–81)
Sex ratio (M:F)	35:14	17:11	5:7
Preoperative weight (kg)	69·9	69·2	65·1
Non-smoking	28 (57)	16 (57)	8 (67)
Alcohol abuse	3 (6)	5 (18)	1 (8)
Coexisting cardiac disease			
Angina pectoris	8 (16)	2 (7)	2 (17)
Previous myocardial infarction	5 (10)	2 (7)	2 (17)
Congestive cardiac failure	2 (4)	0 (0)	2 (17)
Hypertension	14 (29)	7 (25)	0 (0)
Coexisting pulmonary disease			
Restrictive	1 (2)	1 (4)	0 (0)
Obstructive	2 (4)	1 (4)	0 (0)
Chronic bronchitis	4 (8)	2 (7)	1 (8)
Other pulmonary disease	0 (0)	2 (7)	1 (8)
Other coexisting disease			
Diabetes mellitus	3 (6)	1 (4)	0 (0)
Miscellaneous	6 (12)	3 (11)	2 (17)
Loss of weight over 5 kg in 3 months	13 (27)	12 (43)	2 (17)

Values in parentheses are percentages

During the operation an attempt was made to excise regional lymph nodes (i.e. N_1 and N_2 nodes), although a strict D_2-lymphadenectomy was not attempted[11,12]. All total gastrectomies were combined with splenectomy, although pancreatic resection was avoided if possible[13]. Subtotal gastrectomy included complete clearance of lymph nodes along the hepatic artery and the coeliac axis and the entire lesser curvature of the stomach. Therefore, a selective gastric vagotomy was always performed, although the spleen was not removed. All reconstructions used a 50–60-cm retrocolic Roux-en-Y loop of jejunum. The reservoir was fashioned in an S shape from the proximal end of the Roux-en-Y limb, with each limb 10–12 cm long. The distance from the aboral part of the reservoir to the enteroanastomosis was at least 40 cm. All the anastomoses and the reservoirs were hand sutured with absorbable suture material.

Paper accepted 4 December 1995

Pressure–volume recordings

The study protocol included endoscopy at 6 and 12 months after operation. In a subset of the study population, the biomechanical characteristics of the reconstructions were investigated, on an outpatient basis after an overnight fast 3, 6 and 12 months after operation. The aim was for six consecutive patients to be included in each study group, in whom repetitive investigations at all occasions were obtained, but only four patients who accepted all investigations could be recruited in the subtotal gastrectomy group. The technical details of these pressure–volume recordings have been presented elsewhere[14]. In patients with a straight Roux-en-Y oesophagojejunostomy, the balloon was positioned with its proximal end about 5 cm aboral to the oesophagojejunostomy; in the other patients the balloon was positioned in the pouch or in the gastric remnant, as checked by endoscopy.

Table 2 Tumour status and histopathological features in patients with gastric carcinoma treated by total or subtotal gastrectomy

	Roux-en-Y ($n = 49$)	Gastric substitute ($n = 28$)	Subtotal gastrectomy ($n = 12$)
Tumour type			
Adenocarcinoma (diffuse type)	30 (61)	15 (54)	7 (58)
Adenocarcinoma (intestinal type)	13 (27)	6 (21)	5 (42)
Adenocarcinoma (mixed type)	2 (4)	1 (4)	0 (0)
Adenocarcinoma (linitis plastica)	2 (4)	2 (7)	0 (0)
Lymphoma or sarcoma	2 (4)	4 (14)	0 (0)
Depth of growth			
T_1 (mucosa, submucosa)	12 (24)	7 (25)	3 (25)
T_2 (muscularis, subserosa)	26 (53)	15 (54)	7 (58)
T_{3-4}	11 (22)	6 (21)	2 (17)
Nodal status			
N_0	27 (55)	17 (61)	9 (75)
N_1	14 (29)	6 (21)	2 (17)
N_2	8 (16)	5 (18)	1 (8)

Values in parentheses are percentages

Dietary intake

Before and after discharge from the hospital, patients were repeatedly instructed by an experienced dietitian to increase the intake of energy and nutrient-rich foods, to increase meal frequency, to separate solid and liquid food items, and to chew carefully. A 4-day food record was completed at home 3, 6 and 12 months after operation.

Two weekends were included in the recording period to observe variation in food intake that may occur between weekday and weekend food consumption patterns. When returning the food record, the patient was asked to clarify household measures used and a check was made for incomplete recording. Food records were converted from household measures to gram weights and nutrient values according to national food consumption tables[15,16]. The weight of the main meal each day was converted to decilitre (100 ml) measures to determine portion volume.

Faecal nitrogen loss (N_F) was measured together with urinary excretion (N_U) over 3 days in 59 patients. Dermal loss (N_D) was estimated at 1 g per day[17]. Protein loss was subsequently calculated from the formula $6{\cdot}25 \times (N_F + N_U + N_D)$ and then compared with the reported protein intakes 6 and 12 months after gastrectomy.

One indirect way of validating the techniques used to estimate nutritional intake was to record body-weight, related to the estimated energy consumption multiplied by a constant. This constant takes into consideration the energy expenditure of the individual subject. The value of 1·5 was chosen as an arbitrary factor based on the rough estimate that patients' energy consumption and expenditure compared fairly well with that of people doing light white-collar work[18–20].

To compensate for changes in postoperative weight it was decided to relate food intake during the postoperative study period to the preoperative weight level, as an undernourished but weight-stable postoperative patient might report a false accurate food intake if calculated per kilogram of actual body-weight.

Statistical analysis and ethics

The study protocol was approved by the local ethics committee and informed consent was obtained from each patient.

Table 3 Postoperative complications and events in patients undergoing gastrectomy

	Total series ($n = 89$)	Roux-en-Y ($n = 49$)	Gastric substitute ($n = 28$)	Subtotal gastrectomy ($n = 12$)
Mean (range) postoperative hospital stay (days)	24 (0–97)	23 (1–97)	28 (0–169)	22 (8–52)
Anastomotic leakage				
Shown radiographically	4 (4)	2 (4)	2 (7)	0 (0)
Necessitating reoperation	2 (2)	1 (2)	1 (4)	0 (0)
Intra-abdominal abscess	11 (12)	7 (14)	4 (14)	0 (0)
Pancreatic lesions or problems with pancreatic resection	4 (4)	3 (6)	1 (4)	0 (0)
Reoperation for other causes than anastomotic leak	6 (7)	3 (6)	2 (7)	1 (8)
Pneumonia	8 (9)	5 (10)	2 (7)	1 (8)
Cardiac complications				
Myocardial infarction	4 (4)	2 (4)	1 (4)	1 (8)
Heart failure	5 (6)	2 (4)	3 (11)	0 (0)
Other complications				
Mild	10 (11)	5 (10)	3 (11)	2 (17)
Severe	12 (13)	7 (14)	2 (7)	3 (25)
Any complication	47 (53)	25 (51)	15 (54)	7 (58)
Death in hospital	3 (3)	2 (4)	1 (4)	0 (0)

Values in parentheses are percentages

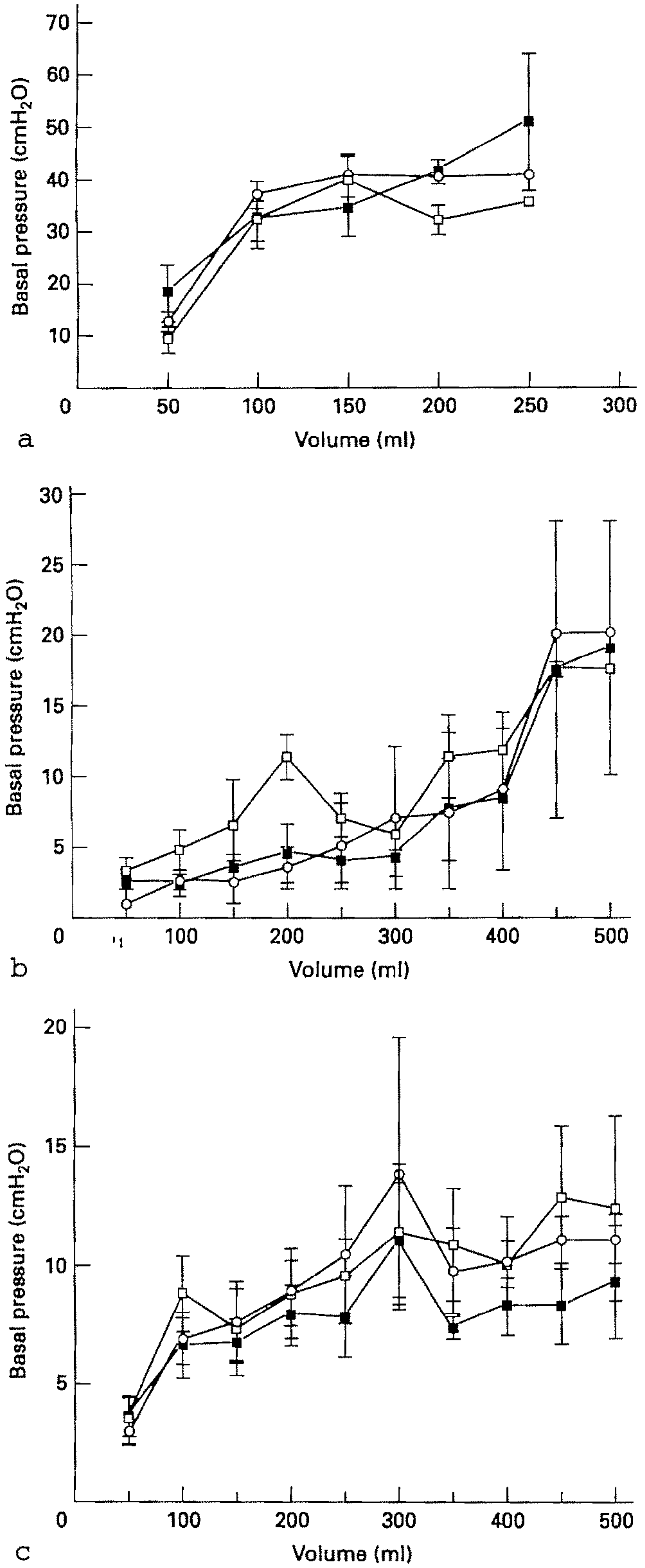

Fig. 1 Intraluminal basal pressure recordings a in the proximal jejunum of patients having a straight Roux-en-Y oesophagojejunostomy ($n = 6$), b in the gastric reservoir after total gastrectomy and gastric substitute formation ($n = 6$) and c in the gastric remnant after subtotal gastrectomy ($n = 4$) during instillation of different volumes into the intraluminal balloon. Values are mean(s.e.m.) at 3 (○), 6 (□) and 12 (■) months after operation

Randomization was carried out by use of sealed envelopes at the time when the operating surgeon considered that resection with curative intent was feasible.

Analysis of data was by the χ^2 method, regression analysis and Student's *t* test where applicable. $P<0·05$ was considered significant.

Results

Histopathological details of the resected specimens and clinical features are shown in *Tables 1* and *2*. The tumour characteristics were similar in the three study groups, although patients having subtotal gastrectomy had more carcinomas of the intestinal type. Postoperative complications are listed in *Table 3*, demonstrating few serious complications. No difference in the complication rate was recorded between patients with and without a gastric pouch. Only two patients had to be re-operated on for leakage from the oesophagojejunostomy, but a further two had leakage from the closed duodenal bulb. Three patients died after operation, which represents a hospital mortality rate of 3 per cent.

At endoscopy 6 and 12 months after operation, a fibrous stricture, oesophagitis or other abnormal findings of the oesophagojejunostomy were not observed in any patient.

The reservoir function of the gastric remnant and substitute was evidenced by a stable, low, basal pressure when up to 400 ml of water was infused into the balloon. Further increment of the balloon volume evoked discomfort and also a pressure rise (*Fig. 1*). No apparent change occurred from 3 to 12 months. On the other hand, in patients having total gastrectomy the basal pressure rose to a level of 35 cmH$_2$O after infusion of 100 ml water into the balloon ($P<0·05$). Maximum recorded pressure amplitudes during the different distension volumes followed a similar pattern. In patients undergoing total gastrectomy the maximal basal pressure and pressure amplitudes were significantly higher ($P<0·05$) than in those having a gastric pouch or subtotal gastrectomy, with a corresponding reduction in maximum tolerated volume (*Fig. 2*).

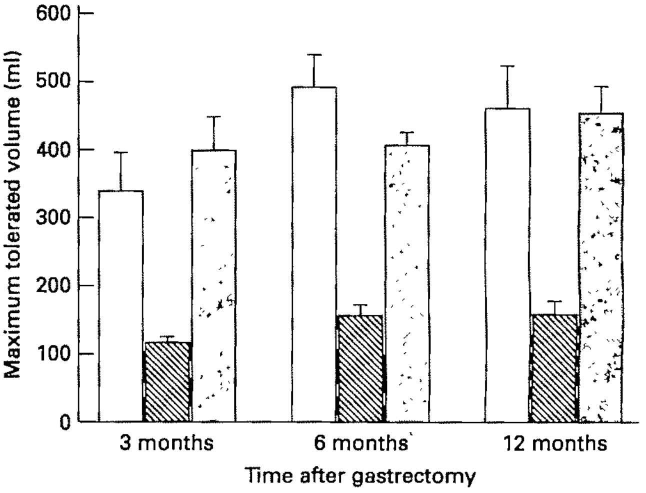

Fig. 2 Maximum tolerated volume at 3, 6 and 12 months after operation. Values are mean(s.e.m.). □, Subtotal gastrectomy; ▨, Roux-en-Y oesophagojejunostomy; ░, total gastrectomy with gastric reservoir

Observed weight changes during the first postoperative year are given in *Table 4*, showing a 10 per cent weight loss during the early postoperative period, whereafter body-weight stabilized.

When assessing the reported protein intake in relation to estimated losses, reported intakes were somewhat higher than calculated losses. At 6 months after operation protein intake was 78·6 g per day compared with an estimated loss of 74·2 g, and the corresponding values at 12 months were 77·4 and 73·1 g respectively.

Patients with an energy intake corresponding to more than 1·5 times the basal metabolic requirement (BMR) had weight gain 3–12 months after operation, whereas those with an intake of less than 1·5 times the BMR lost weight during the same period (*Fig. 3*).

The energy intake 3 months after gastrectomy was significantly ($P<0·05$) lower in patients with subtotal gastrectomy. This remained low when assessed after 12 months (*Table 4*). As there were comparatively more women in the subtotal gastrectomy group, a subgroup analysis of women was carried out to elucidate whether these differences could be explained by imbalances in sex. Similar differences persisted when the analysis was carried out, although this could be statistically substantiated at 3 months only between those with a substitute and a gastric remnant because of limited sample size ($P<0·02$). Total energy intake in relation to preoperative body-weight was 101, 133 and 90 kJ/kg for the Roux-en-Y group, those with a gastric substitute and those having subtotal gastrectomy respectively when assessed at 3 months. The corresponding values at 6 and 12 months were 116, 123 and 115 kJ/kg and 107, 133 and 95 kJ/kg respectively. When the major food constituents were analysed separately a similar relationship was found between protein, fat and carbohydrate intake in gastrectomized patients, as previously noted in the reference population of Sweden[16].

Table 4 Weight loss compared with preoperative weight and food intake assessed in relation to preoperative body-weight at 3, 6 and 12 months after operation

Time after operation (months)	No. of observations	Energy intake* (kJ/kg)	Weight loss* (kg)
Gastric substitute			
3	23	122·5(7·6)	7·8(1·2)
6	24	123·9(6·5)	7·6(1·8)
12	20	120·5(5·5)	6·9(2·1)
Roux-en-Y			
3	30	123·6(8·3)	7·4(1·4)
6	32	131·1(7·8)	8·5(1·1)
12	33	131·9(7·6)	9·0(1·6)
Subtotal gastrectomy			
3	8	91·7(10·8)	5·2(1·4)
6	9	121·7(13·2)	5·7(1·8)
12	8	106·0(12·0)	6·6(3·2)

*Values are mean(s.e.m.)

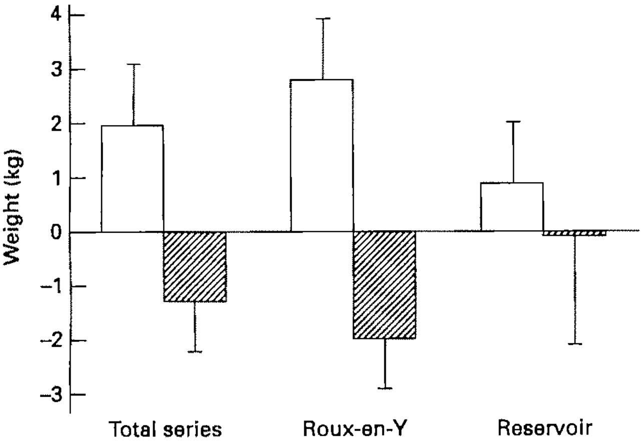

Fig. 3 Mean(s.e.m.) weight changes after gastrectomy related to eating habits and basal metabolic rate (BMR). These calculations were based on relevant intakes 3–12 months after gastrectomy. □, More than 1·5 times BMR; ▨, less than 1·5 times BMR

Meal sizes at 3 months after operation were calculated to be 530, 490 and 410 ml respectively in the total gastrectomy, gastric substitute and subtotal gastrectomy groups. Similar values were found when meal size was estimated at 12 months (590, 550 and 510 ml respectively).

Patients who had subtotal gastrectomy and or a gastric pouch complained more frequently ($P<0·03$) of postprandial symptoms as the major cause of reduced food intake than those who had a straight Roux-en-Y oesophagojejunostomy following total gastrectomy (15 *versus* 42 per cent). These adverse symptoms were mainly abdominal pain, bloating, diarrhoea and dumping.

Discussion

The two major threats to patients surviving gastrectomy for gastric carcinoma are, first, the risk of tumour recurrence and, second, malnutrition occurring as a consequence of gastrectomy[21]. Traditionally, malnutrition after total gastrectomy was attributed to malabsorption caused by bacterial overgrowth, damage to the mucosa of the upper small intestine, relative pancreatic insufficiency and shortened small-bowel transit time. However, clinical observations suggest that the passage of food through the small intestine is essentially normal after total gastrectomy and in fact is sometimes reported to be retarded[8,22]. On the other hand, reconstruction of the alimentary canal after total gastrectomy, which bypasses the duodenum, would have the potential to cause malabsorption of fat by other mechanisms as well[23,24]. The clinical consequences of losing the reservoir function of the stomach are even less clear. Rapid weight loss is experienced by many patients shortly after total gastrectomy and an important mechanism behind this phenomenon is low energy intake[7,9]. A correlation was also found in the present study between energy intake and postoperative weight development. Other reasons for low intake, however, include lack of appetite, dyspepsia, altered intestinal motility, dysphagia and/or early postprandial satiety. Dysphagia caused by stricturing of the oesophagojejunostomy may have a considerable impact on energy intake. This was excluded as a cause in the present patients by endoscopic examination.

There are different ways to establish and record eating habits and dietary intake. One precise, but cumbersome, laborious and costly technique is to study the patients in metabolic ward conditions. Another, more pragmatic, approach is to investigate patients on an outpatient basis, obtaining a 4-day food record. This method has the advantage that it estimates nutrient intake over a reasonably long period of time and recordings can be repeated. The technique also allows determination of specific nutrients, which are present in different food items. However, the validity of these estimates depends greatly on the ability of the patient to follow the guidelines and educational information offered by the clinical dietitian. The validity of the method used in the present study has been documented in large population studies[25,26]. If food intake is considered in relation to BMR, weight development during a particular period can be predicted by multiplying a constant with the BMR. Patients with a food intake greater than 1·5 times the BMR showed a weight gain 3–12 months after operation, whereas those with an intake below 1·5 times the BMR showed further weight loss.

The present study provides two pieces of information of particular clinical significance with respect to nutritional adaptation after gastrectomy. First, weight loss occurred during the first 3 months after surgery. For reasons that are not clear, a lower intake of carbohydrate, protein and fat was observed in patients who had subtotal gastrectomy than in those having total gastrectomy. To prevent this weight loss, nutritional support and education should consequently concentrate on interventions in the early postoperative period to optimize the potential for success, irrespective of the surgical procedure.

The recorded differences in energy intake between those having subtotal or total gastrectomy is somewhat unexpected, but may be influenced by the fact that more women were randomized to have subtotal gastrectomy, as dietary intake is lower in women than in men. To clarify this issue, a further subgroup analysis was performed on the entire material: the differences in dietary intake could not be explained purely on a sex basis. However, patients having subtotal gastrectomy or gastric replacement by a jejunal pouch complained more frequently (42 *versus* 15 per cent) of postprandial symptoms as the major cause of impaired food intake. The reasons for the increased frequency of adverse postprandial complaints are unknown.

The second area of interest is related to the type of reconstruction after gastrectomy. It has been alleged that construction of a reservoir or leaving a gastric remnant in place after gastrectomy might allow the patient to consume larger meals and thereby improve food intake, with clinical consequences of improved general well-being and restored quality of life[10,27–29]. Remarkably good results have been presented in uncontrolled series, in which specific types of intestinal reservoir have been assessed. This was not confirmed, however, in the present controlled clinical trial. It may be that the design of the reservoir is of particular significance for the subsequent clinical outcome. However, the results of controlled clinical trials do not support this argument[30].

Soon after gastrectomy the biomechanical properties of the gastric jejunal substitute were seen to be similar to those of a gastric remnant after subtotal gastrectomy. Despite this, these patients did not report larger meals or improved energy consumption compared with those having a simple Roux-en-Y oesophagojejunostomy. However, it may be that the present series did not contain a sufficient number of patients to establish a significant difference with acceptable statistical power.

A gastric reservoir constructed after gastrectomy does not improve the nutritional intake compared with that seen following a straight Roux-en-Y oesophagojejunostomy. On the contrary, because patients with a reservoir reported postprandial symptoms as a major cause of reduced food consumption, the question has to be raised whether the principle of retaining a gastric remnant, if possible, or of substituting it, should be abandoned. Continued follow-up is needed to determine the long-term benefit of these procedures.

Acknowledgements

This work was supported by grants from the Swedish Medical Research Council (17X-760).

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British Journal of Surgery 1996, 83, 1144–1147

Benefits of D_2 lymph node dissection for patients with gastric cancer and pN_0 and pN_1 lymph node metastases

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A retrospective immunohistological analysis of 100 patients with pT_{1-3} N_0 and pT_{1-3} N_1 gastric adenocarcinoma demonstrated a high frequency of micro-involvement in the removed lymph nodes. The presence of three or more tumour cells in more than 10 per cent of the lymph nodes was of significant prognostic value in the pN_0 cases. Multivariate analysis identified micro-involvement as an independent prognostic factor. The results explain why patients benefit from lymphadenectomy even if the removed lymph nodes are not involved by tumour (pN_0) in routine histological examination. The frequent occurrence of micro-involvement is a strong argument favouring routine D_2 lymph node dissection in gastric cancer surgery in patients with lymph node metastasis.

Recently published studies[1–3] conclude that patients with Union Internacional Contra la Cancrum (UICC) tumour stages II and IIIA benefit from a D_2 lymph node dissection. An exact analysis of subgroups[1] demonstrates that patients without lymph node metastasis (pN_0) on routine histological examination or with early lymph node metastasis (pN_1) have significantly better survival with D_2 lymph node dissection. These results are unexpected, because from a theoretical point of view it is surprising that patients without lymph node metastasis or early lymph node spread should benefit from surgical dissection of a large number of apparently uninvolved lymph nodes. The present retrospective analysis attempts to explain this phenomenon. The authors have reanalysed the surgical specimens of 100 patients who had a $\mathrm{pT}_{1-3}\,\mathrm{pN}_0$ or $\mathrm{pT}_{1-3}\,\mathrm{pN}_1$ gastric carcinoma on routine histological examination, employing immunohistochemical techniques to identify small numbers of tumour cells.

Patients and methods

A total of 100 patients operated on between 1982 and 1988 with resectable gastric carcinoma for whom adequate clinical information was available (median follow-up 6·6 (range 3·8–10·7) years). The procedure used was according to the recommendations of the Japanese Research Society for Gastric Cancer[4]: all 53 patients with a tumour of the diffuse or mixed Laurén growth pattern underwent total gastrectomy regardless of the location of the tumour; of the 47 patients with an intestinal Laurén tumour type, those with pT_1 or pT_2 tumours in the antrum underwent subtotal gastrectomy; for intestinal-type carcinomas in the upper third of the stomach, the distal portion of the oesophagus was also resected (*Table 1*).

An extended (D_2) lymph node dissection was performed in all patients to remove not only compartments I and II, but also lymph node stations 12 (hepatoduodenal) and 13 (retroduodenal)[4,5]. None of the included patients was treated before or after operation with either chemotherapy or radiotherapy.

Histopathological staging according to the tumour node metastasis (TNM) classification of the UICC (fourth edition)[6] is shown in *Table 1*. None of the patients had distant metastases at the time of surgery and all tumours were completely resected (UICC R_0). According to the German grading scheme 24 tumours were moderately differentiated (G_2) and 76 were poorly differentiated (G_3). A total of 3377 lymph nodes was dissected from the 100 gastrectomy specimens, a median of 32 (range 4–106) nodes per patient.

Table 1 Clinical and pathological features of 100 patients with gastric adenocarcinoma

Median (range) age (years)	65 (34–83)
Sex ratio (M:F)	58:42
Type of gastrectomy	
Subtotal	32
Total	68
Median (range) no. of removed lymph nodes	32 (4–106)
Grading	
G_1	0
G_2	24
G_3	76
Laurén type	
Intestinal	47
Diffuse or mixed	53
Depth of invasion	
pT_1	37
pT_2	48
pT_3	15
Lymph node involvement	
pN_0	62
pN_1	38

All specimens were formalin fixed and paraffin embedded. One section from each lymph node was stained with haematoxylin and eosin and with periodic acid–Schiff. One additional serial section from each lymph node was stained immunohistologically using AE1–AE3[7] (20:1 mixture of AE1 to AE3; Boehringer, Mannheim, Germany), a pool of monoclonal antibodies that is reactive with a broad spectrum of human keratins. Since AE1–AE3 reacts positively with mesothelium as well as epithelium (tumour cells), an additional antibody, BerEP4 (IgG1; Dako Diagnostika, Hamburg, Germany), was used on a selected group of 100 sections. BerEP4 reacts with epithelial elements such as gastric adenocarcinoma, but does not react with mesothelial cells[8,9].

The antibody reactions were developed with the alkaline phosphatase–antialkaline phosphatase technique[10]. The immunohistochemical investigation was limited to one slide preparation per lymph node to simulate routine histological procedures[11].

Paper accepted 1 October 1995

Microinvolvement was defined as the presence of individual tumour cells in the sinus or medulla of the lymph node without a surrounding stromal reaction. In contrast, any group of tumour cells with a stromal reaction was classified as a metastasis, and such a deposit less than 2 mm in size as a micrometastasis.

In addition, clinical and pathological data for these cases were collected by the participating surgeons and pathologists according to a standardized protocol. The data were then evaluated using the BMDP software package (BMDP Statistical Software, Los Angeles, California, USA) and the CDC computer system of the Leibniz Rechenzentrum, Munich. Prognostic factors were evaluated by multiple stepwise regression analysis using the Cox model[12]. Survival data were analysed with the Kaplan–Meier survival model[13] and are given as observed overall survival including postoperative deaths. The log rank test was used to assess statistical differences between groups[14]. The level of significance was set at 5 per cent ($P < 0{\cdot}05$).

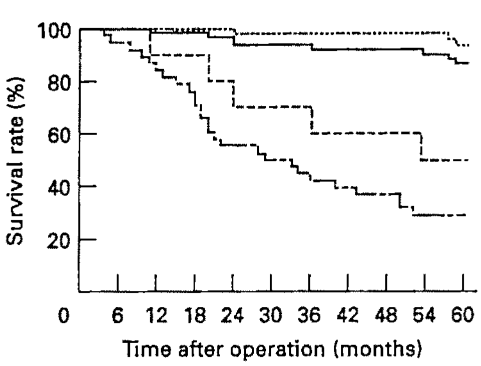
Results

Two patients had an immunohistochemically detected micrometastasis (one lymph node in each patient), which had not been identified by routine histology. One of these patients had a pT_1 early carcinoma of the intestinal type with submucosal invasion (pT_{1sm}), and one a pT_3 carcinoma of the diffuse type. Microinvolvement in sections of regional lymph nodes was found in 93 of the 100 gastrectomy specimens, in 56 of 62 pN_0 cases (90 per cent) and 37 of 38 pN_1 cases (97 per cent).

Analysis of the occurrence of microinvolvement in relation to tumour characteristics showed a statistically significant increase in the incidence of microinvolvement in pT_3 in comparison with pT_1 tumours, in non-intestinal (mixed and diffuse) compared with intestinal Laurén types, and in patients with lymph node involvement (pN_1 greater than pN_0) (*Table 2*). Microinvolvement was always more frequent in patients with G_3 tumours than in those with G_2 tumours, but this difference was only marginally significant.

Univariate analysis demonstrated shorter survival of patients without lymph node metastasis but with microinvolvement by three or more tumour cells in more than 10 per cent of the removed lymph nodes, compared with the other patients in the pN_0 category ($P < 0{\cdot}0001$), but better survival than those with lymph node metastases ($P < 0{\cdot}001$) (*Fig. 1*).

Survival data were examined statistically in relation to the following set of covariables: depth of tumour invasion (pT), lymph node involvement (pN), number of lymph nodes involved by tumour, grading (G), Laurén classification, sex, number of lymph nodes with microinvolvement and number of tumour cells of microinvolvement per lymph node. The variables found to be statistically significant were then ranked in descending order of their significance level. For the entire set of 100 patients (pN_0 and pN_1) (*Table 2*) lymph node involvement (pN) was the most important prognostic factor, followed by depth of tumour invasion (pT). The ratio of involved to removed lymph nodes (lymph node ratio) was the third most important prognostic factor, but was significant only if more than 16 per cent of the dissected lymph nodes per case contained tumour. Microinvolvement was the fourth ranking prognostic factor, but was significant only if three or more cells in more than 6 per cent of the lymph nodes of the specimen were involved (one section of each lymph node). Microinvolvement never had an adverse prognostic impact as great as that of lymph node metastasis, even when the nodes from the cases most heavily involved by microinvolvement were used for comparison (5-year



No. at risk						
pN_0	62	61	58	57	55	44
$pN_0 \leq 10$ per cent microinvolvement	52	52	51	51	49	39
$pN_0 > 10$ per cent microinvolvement	10	9	7	7	6	4
pN_1	38	32	21	16	13	7

Fig. 1 Survival in relation to involvement of removed lymph nodes. --------, pN_0 (all patients); ––––, pN_0 with three or more tumour cells per lymph node section and more than 10 per cent of sampled nodes with microinvolvement; ———, pN_0 with 10 per cent or less microinvolvement; —— – ——, pN_1. $P < 0{\cdot}0001$ (pN_0 *versus* pN_1, pN_0 with 10 per cent or less microinvolvement *versus* pN_0 with more than 10 per cent microinvolvement), $P = 0{\cdot}001$ (pN_0 with more than 10 per cent microinvolvement *versus* pN_1) (log rank test)

Table 2 Frequency of lymph node metastasis and microinvolvement according to the tumour node metastasis subgroup of 100 patients with gastric adenocarcinoma

TNM subgroup	No. of patients	Removed lymph nodes	Lymph nodes with metastasis (%)	Lymph nodes with microinvolvement (%)	Microinvolvement (%)	
					No. of tumour cells < 3	No. of tumour cells ≥ 3
T_{1m} N_0	13	451	—	13·8	12·2	1·6
T_{1sm} N_0	22	574	—	15·3	11·5	3·8
T_{1sm} N_1	2	77	2·6	11·7	11·7	—
T_2 N_0	25	888	—	21·9	13·7	8·2
T_2 N_1	23	850	10·5	25·5	15·5	10·0
T_3 N_0	2	62	—	45·2	21·0	24·2
T_3 N_1	13	475	16·2	29·0	10·7	18·3
Total	100	3377	5·0	21·8	15·7	8·6

TNM, tumour node metastasis; m, mucosal invasion; sm, submucosal invasion

Table 3 Ranking of prognostic factors by multivariate analysis

	P
All cases ($n = 100$)	
1 pN category	<0.0001
2 pT category	0·0005
3 Lymph node ratio more than 16 per cent	0·026
4 Microinvolvement: (≥ 3 tumour cells in more than 6 per cent of sampled lymph nodes)	0·026
pN_0 cases ($n = 62$)	
1 Microinvolvement: (≥ 3 tumour cells in more than 10 per cent of sampled lymph nodes)	0·0009
pN_1 cases ($n = 38$)	
1 pT category	0·026
2 Lymph node ratio more than 16 per cent	0·028

survival rate of 29 per cent for the 38 pN_1 patients compared with 69 per cent for pN_0 patients with at least one lymph node with more than 15 tumour cells of microinvolvement, $P = 0.007$, Log rank test).

In the pN_0 group (*Table 3*) microinvolvement was the only significant prognostic factor, but only when the threshold of three or more tumour cells in more than 10 per cent of the lymph node sections was exceeded. When the pN_0 and in pN_1 groups were analysed separately, it was found that, for the pN_1 patients, tumour invasion (pT) was the most significant factor for prognosis, followed by the number of lymph nodes with metastases. Microinvolvement was not a significant factor in this group of patients.

Discussion

Lymph node metastasis in gastric cancer develops over a long period in a stepwise fashion and follows the anatomy.

The prognosis of a patient should deteriorate gradually when lymph node metastasis occurs in a stepwise manner. Many studies have shown that the prognosis deteriorates in patients with six to eight positive lymph nodes[15,17,18]. With an adequate D_2 lymph node dissection about 30 to 40 lymph nodes can be removed[1,3,19], so it should be possible to excise many more nodes than those apparently involved. To achieve an improvement in prognosis, no more than 20 per cent of the surgically removed lymph nodes should be involved, i.e. no more than six to eight lymph nodes of 30 to 40 removed lymph nodes[15,16].

It has been shown that patients with UICC tumour stages II and IIIA benefit from D_2 lymph node dissection[1–3]. In the subgroup analyses, the survival advantage was most pronounced in patients with absent (pN_0) or early (pN_1) lymph node metastasis on routine histological examination. Dissection of a large number of apparently uninvolved lymph nodes appears to be important for improvement of the prognosis in these patients, but it is not clear why lymph nodes that are not obviously tumour positive have to be dissected.

To answer this question, the material was reanalysed by means of immunohistochemistry, looking in regional lymph nodes for the presence of tumour cells that were not detected by routine histological methods. Several studies in the past have demonstrated that immunohistochemistry is able to detect far more gastric tumour cells in lymph nodes than are seen by routine methods[20,21]. The present study is representative for several reasons. First, a large number of lymph nodes (3377) was available for study, obtained by a standardized D_2 lymph node dissection procedure[4,5]. Second, the large amount of clinical and pathological data available from this group of patients allowed a detailed statistical comparison of lymph node findings to be made. Last, and perhaps most importantly, lymph nodes with deposits of tumour without a surrounding stromal reaction (microinvolvement) were carefully distinguished from those with true micrometastases, i.e. tumour cells with a stromal reaction.

The present results show that microinvolvement occurs very frequently in the regional lymph nodes of patients with gastric carcinoma. Certain features of the primary tumour correlated with the likelihood of microinvolvement. These included the depth of tumour invasion (pT), presence of lymph node metastases (pN), and tumour grade (G). Mixed or diffuse Laurén types of carcinoma also showed an increased tendency for microinvolvement, which might be explained by the lack of adhesion between the cells of these tumours[22].

These results also support the distinction between microinvolvement and micrometastasis. From the analysis of the survival data in these patients, it can be clearly seen that metastasis to regional lymph nodes in gastric carcinoma has a much more adverse impact on prognosis than microinvolvement. In these patients, microinvolvement was of no further prognostic importance once metastasis had been identified (pN_1) and in pN_0 cases was of importance only above a certain threshold (three or more tumour cells per lymph node in more than 10 per cent of the sampled lymph nodes per case). This indicates that microinvolvement is a 'premetastatic phase' of tumour cell dissemination in which tumour cells have arrived in the lymph node through the circulation but are presumably not yet able to maintain themselves through interactions with the surrounding stroma.

Particularly in apparently pN_0 patients, it is surprising that removal of regional lymph nodes should have an impact on prognosis. The results of this study provide an explanation for this observation, since it was found that a significant number of tumour cells is present in the regional lymph nodes of patients with gastric carcinoma even when routine histological methods show no evidence of nodal metastasis (pN_0). Removal of these nodes would diminish or eliminate these remaining tumour cells and would thus be expected to result in improved prognosis for the patient. The frequent occurrence of microinvolvement is a strong argument favouring routine D_2 lymph node dissection in surgery for gastric carcinoma in the early phase of lymph node metastasis.

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British Journal of Surgery 1996, 83, 1148–1151

Prognostic value of monolayer culture patterning in primary cell culture of oesophageal cancer

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The growth of primary cell cultures of oesophageal cancer was compared with the clinical outcome of patients from whom the cancers were taken. Ninety-three patients underwent curative resection, with no operative deaths, and were divided into three groups according to the monolayer culture pattern of the primary cell culture: culture from 43 patients (46 per cent) grew no malignant cells (group 1), 21 (23 per cent) produced monolayer epithelial growth (group 2) and the rest (from 29 patients) established cell lines (group 3). The 5-year survival rate of patients in group 2 (29 per cent) and group 3 (23 per cent) was significantly lower ($P < 0{\cdot}005$) than that of those in group 1 (51 per cent). Monolayer epithelial growth potential is a significant prognostic factor in patients with oesophageal cancer.

The use of cell culture techniques has been limited by the poor success rate of *in vitro* culture. Thus, the clinical application of cell culture in the determination of tumour growth potential has also been limited. Previous attempts to correlate growth in culture with *in vivo* behaviour in patients with oesophageal carcinoma revealed that the establishment of cell lines was a significant prognostic factor in oesophageal cancer[1]. However, the length of time it takes to establish cell lines with this methodology has inevitable disadvantages. Over the past 7 years, 36 oesophageal cancer cell lines (KYSE series[2,3]) have been established from human oesophageal tumour specimens: 21 of these were established from 50 consecutive surgical specimens and 15 were recently added oesophageal cancer cell lines. During this period it was noticed that patients whose cancer cells showed epithelial growth in monolayer culture had a poor prognosis. This newly designated group with epithelial growth had previously been included in the non-established cell line group[1]. The present study represents a further developmental stage in the investigation of the growth potential of oesophageal cancer cells *in vitro*. Statistical significance was not obtained in the previous research because of lack of consistency in the patients' background information combined with the limited number of cases available.

The detection of monolayer epithelial growth in primary culture is a simple method and can be accomplished in 1–2 weeks. If monolayer epithelial growth was found to be a significant prognostic factor, this would allow the surgeon to consider other treatment options.

To evaluate the predictive value of monolayer epithelial growth in primary cell culture as an indicator of biological malignancy, the *in vitro* growth of primary cell cultures of oesophageal cancers was compared with the clinical prognosis of patients from whom the cancers were taken.

Patients and methods

Patients

Tumour samples were taken from 120 consecutive patients who had undergone oesophageal resection from 1986 to 1992. The same operative techniques were used as previously described[4]: subtotal oesophagectomy with lymph node dissection reconstructed with retrosternal gastric tubes. Three patients with cervical oesophageal cancer received free jejunal graft interposition. Each patient's clinical status was classified from stage 1 to 4 according to the pathological tumour node metastasis (pTNM) classification system[5]. Preoperative and postoperative therapy was administered according to clinical stage[6,7]. In brief, preoperative chemotherapy consisted of low doses (50 mg per body) of *cis*-diamminedichloroplatinum (II) (CDDP) and postoperative chemotherapy was determined by the histological stage of the resected oesophagus. Preoperative radiotherapy was not performed routinely, except in patients who had been transferred from other departments; postoperative radiotherapy consisted of 50·4 Gy of irradiation.

Cell culture

Culture samples were obtained from resected specimens in the operating room. Details of the culture methods and cell characterization have been described previously[1–3]. In brief, the samples were taken from the mucosal surface and washed four times with minimum essential medium (Nissui, Tokyo, Japan) containing amphotericin B 10 μg/ml. Necrotic or haemorrhagic regions, associated muscle and fat were removed. The mean size of tumour sample taken from resected oesophagus was 1·0 cm^3. The cancer tissue was minced with sharp scissors into pieces approximately 0·5 mm in diameter, and a crude cell suspension was made by pressing the minced tissue through a stainless steel mesh. This cell suspension was dispersed into 60-mm cell culture dishes together with 6 ml culture medium for primary culture, and covered with a 90-mm Petri dish to avoid inversion. Ham's F12 (Nissui) and RPMI 1640 medium (GIBCO, Grand Island, New York, USA) containing 20 per cent fetal calf serum (FCS; Flow Laboratories, Rockville, Maryland, USA), penicillin 100 units/ml and gentamicin 2·5 μg/ml were used for the primary culture. The cultures were maintained at 37°C in a humidified atmosphere containing 5 per cent carbon dioxide until confluent. The cultures were examined daily and the medium was usually renewed twice weekly.

Cell culture pattern

The pattern of monolayer culture was examined by phase-contrast microscopy. Growth patterns were classified in terms of the single fastest growth rate rather than determining the mean growth rate of all samples. Despite efforts to encourage cultivation of cancer cells, in a few cases only normal epithelial growth was observed. Cultures of normal human oesophageal cells and oesophageal carcinoma cells are morphologically

Paper accepted 31 October 1995

distinguishable when examined by phase-contrast microscopy[8]. Normal human epithelial cells are polygonal, uniform in appearance and never pile up, whereas oesophageal carcinoma cells are pleomorphic, vary greatly in size and shape, and demonstrate a tendency to pile up in an organized fashion and to be packed together. After 14 days no further growth of cancer cells was detected, so a maximum regrowth period of 14 days was established. Fibroblast overgrowth was controlled by differential trypsinization and scraping. Initial cell passage was performed when rapid tumour cell growth was observed. After the cells had adapted to culture conditions they were maintained in Ham's F12 and RPMI 1640 medium with 2 per cent FCS.

Statistical analysis

Differences between groups of patients were compared with the Kruskal–Wallis test. The cumulative survival curves for patient groups were calculated by the Kaplan–Meier method[9] and compared with log rank testing[10]. Stepwise regression using the Cox proportional hazard model[11] was applied to estimate the survival rate by compensating for differing factors in patient background. The variables used in the Cox regression analysis were as follows: monolayer culture patterning, age, sex, T stage, N stage, M stage, number of lymph node metastases, number of culture dishes, diameter of tumour, preoperative chemotherapy and preoperative radiotherapy. The last four variables were selected because of their possible influence on primary cell culture. For the purpose of regression analysis, a score was assigned to each variable in the order shown in *Table 1*. The assigned scores of the 'sex' variable were: male, 1; female, 2. The optimal categorization of two of the variables (the number of lymph node metastases and culture dishes) was determined according to Akaike's information criteria (AIC)[12]. AIC values were calculated with following formula:

$$\mathrm{AIC} = -2 \log(\text{maximum likelihood}) + 2\,(\text{parameter})$$

Table 1 Patient details

	Group 1 ($n = 43$)	Group 2 ($n = 21$)	Group 3 ($n = 29$)	P*
Mean(s.d.) (range) age (years)	66·0(9·7) (43–84)	65·3(9·6) (49–81)	62·1(10·3) (39–81)	
Sex ratio (M:F)	34:9	18:3	23:6	
Location of tumour				
Cervical	1	0	5	
Upper intrathoracic	6	2	3	
Middle intrathoracic	27	12	15	
Lower intrathoracic	7	7	6	
Abdominal	2	0	0	
TNM stage				
1	5	1	2	
2a	9	2	5	
2b	9	5	4	0·23
3	15	8	14	
4	5	5	4	
No. of dishes used for primary culture				
≤3	29	8	13	
4–6	8	7	8	0·05
≥7	6	6	8	
No. of lymph node metastases				
Mean(s.d.) (range)	3·8(7·5) (0–43)	8·0(11·3) (0–50)	3·9(4·5) (0–20)	0·06
≤2	28	7	13	
3–7	7	6	11	0·05
≥8	8	8	5	

TNM, tumour node metastasis. *Kruskal–Wallis test

Results

Ninety-three of 120 patients underwent curative resection (no residual tumour existed macroscopically and microscopically, TNM-R$_0$) and there were no operative deaths. The patients comprised 75 men and 18 women aged 43–84 years.

The survival rate of patients from whom cell lines were established ($n = 29$) and that of those from whom cell lines were not ($n = 64$) were compared. The rate was significantly lower in the cell line group ($P = 0{\cdot}02$, log rank test).

Patients were divided into three groups according to the monolayer growth patterns observed by phase-contrast microscopy: group 1 – no malignant cell growth (43 patients); group 2 – epithelial monolayer growth (21); and group 3 – cell line established (29). The clinicopathological and technical backgrounds of the patients are shown in *Table 1*. Group 1 represents normal epithelial cell growth or parenchymal cell growth such as fibroblast and myoblast. There were no contaminated cultures. The term monolayer epithelial growth refers to that stage in the development of the cell when new tumour cells begin to migrate out of any scattered island of tumour cells that has already attached itself to the culture dish (*Fig. 1*). Some carcinoma cells grew from single-cell or small (10–20 cells) clusters. Group 2 represents any level of growth that fell short of establishing a cell line. All cell lines (group 3) were established by undergoing the monolayer epithelial growth process (group 2).

There were no significant differences among the three groups with regard to sex, age, location of lesion, histological type, invasion to the adventitia, number of lymph node metastases, histological stage, or preoperative and postoperative treatment. The only significant difference was in the number of culture dishes used.

The cumulative survival curves of the three groups of patients are shown in *Fig. 2*. Log rank testing indicated that the survival rate of patients in groups 2 and 3 was significantly lower than that of those in group 1 ($P < 0{\cdot}005$). Cox proportional hazard analysis also revealed that a biological staging system based on monolayer culture patterning is a useful and significant prognostic factor ($P = 0{\cdot}0004$), and that this prognostic factor is nearly equivalent to the number of lymph node metastases present ($P = 0{\cdot}0001$) (*Table 2*). TNM

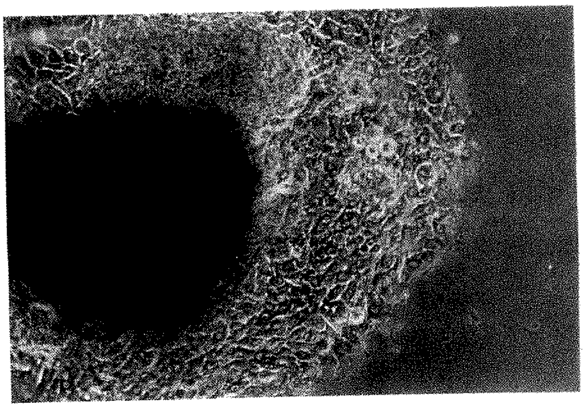
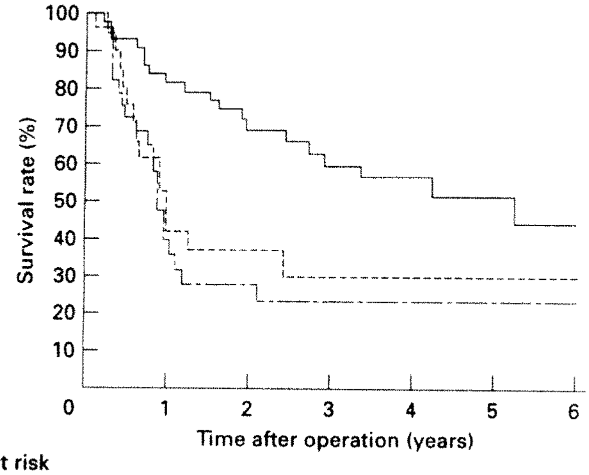


Fig. 1 Phase-contrast view of monolayer culture of the tumour, showing the tumour cell migrating out of the scattered cluster. This phase is designated as the monolayer epithelial growth stage (original magnification × 200)



No. at risk							
Group 1	43	35	30	27	26	25	24
Group 2	21	9	8	7	7	7	7
Group 3	29	12	9	8	8	8	8

Fig. 2 Cumulative Kaplan–Meier survival curves for 93 patients with oesophageal cancer. ———, Patients whose tumour cells did not proliferate in monolayer culture (group 1, $n = 43$); -----, patients whose tumour cells demonstrated monolayer epithelial growth (group 2, $n = 21$); —-—-, patients from whom cell lines were established (group 3, $n = 29$). ($P = 0{\cdot}003$, log rank test)

Table 2 Valuation of variables in predicting survival of 93 patients with oesophageal cancer, according to stepwise regression using the Cox model

Variable	β	Standard error	χ^2	P
No. of lymph node metastases	1·106	0·208	28·175	0·0001
Monolayer culture status	0·447	0·125	12·757	0·0004
Age	0·459	0·149	9·428	0·002
Diameter of tumour	− 0·793	0·324	5·982	0·014
M*	0·596	0·358	2·765	0·096
No. of culture dishes	0·265	0·183	2·096	0·15

*M category of the pathological tumour node metastasis classification

classification and sex were not significant predictors of survival. Other variables studied (preoperative chemotherapy, preoperative radiotherapy and number of culture dishes) had no relation to monolayer culture patterning or its prognostic value.

Discussion

Several attempts to correlate growth in monolayer culture with tumour behaviour *in vivo* in patients with oesophageal carcinoma have yielded inconclusive results[13,14]. Previous studies demonstrated that the ability of cells from an oesophageal cancer sample to establish a successful continuously growing cell line was a significant prognostic factor[1]. In this study the potential of monolayer epithelial growth in predicting patient survival was evaluated.

Two grades of monolayer epithelial growth were subjectively classified: slow or short-term rapid growth (grade 1) and long-term growth but no establishment of a cell line (grade 2). Because of the small number of tumours classified at grade 2 level ($n = 4$), the prognosis of which was grade 1, it was decided to combine grade 1 and 2 tumours into a single group, and to designate it the monolayer epithelial growth group. Interestingly, contrary to expectation, the prognosis of patients in the monolayer epithelial group was poor and equalled that of the cell line group. This suggests that, even the early migration stage, oesophageal cancer cells are associated with a poor prognosis, and this is presently being studied with the use of biopsy samples. Previous studies included patients having non-curative resection, but the present research was limited to those undergoing curative surgery (TNM-R_0). Therefore, monolayer epithelial growth represents the malignant potential after curative oesophagectomy and may be a useful guide for determining the need for postoperative adjuvant treatment.

In this series, despite previous cytotoxic therapy, patients whose tumour cells demonstrated monolayer epithelial growth or continuous cell line development had a poor prognosis. Multivariate analysis, which included the preoperative treatment factor, revealed that preoperative treatment had no effect on the prognostic significance of successful cell culture. The results indicate that, even if the establishment of cell lines was disturbed, monolayer epithelial growth was still related to prognosis in patients with oesophageal cancer. Indeed, although the rate of establishment of the cell lines was decreased by preoperative cytotoxic therapy, this did not affect the ability of the monolayer epithelial growth to show regrowth potential *in vitro*, thus demonstrating that cancer cells which are resistant to cytotoxic therapy exhibit the most aggressive behaviour.

There is no definitive logical explanation for the relationship between monolayer epithelial growth and malignant potential. The monolayer culture environment lacks the supporting three-dimensional extracellular matrix and requires that tumour cells compensate for differences between the synthetic nutrient medium and the body fluids that previously supported growth. Thus, tumour cultures in which monolayer epithelial growth occurs appear to have successfully overcome the difficult problems of adherence and metabolic compensation. Regarding the characterization of tumours, statistical analysis revealed that in cells of malignant potential haematogenous recurrence tended to occur[15]. Preliminary analysis has not revealed any correlation between the cell growth pattern and cell cycle gene expression (CyclinD1, int-2, p53, Rb, p16, p15, p21, HPV, etc., unpublished observations). Only MDM2 gene amplification related to the capacity for monolayer epithelial growth (data not shown), but further analysis is required. This will include the measurement of other previously established parameters that have proved useful in characterizing carcinoma, such as simultaneous measurement of proliferative activity.

Conventional staging systems do not represent the dynamic biological activity of the tumour, but show only a static picture. Therefore, the assessment of cellular kinetics such as proliferation index, cell cycle phases, thymidine labelling and mitotic count may be better estimates of tumour activity in solid tumours[16–19]. Monolayer epithelial growth may represent the global characteristics of adhesive, motile, invasive and reproliferative abilities. Moreover, monolayer epithelial growth can be evaluated within 2 weeks, which is a sufficiently short period to allow its postoperative use. The value of this method lies in its basic simplicity. It requires no complex, costly or potentially harmful technology or instruments, an added advantage being that results may be successfully achieved with a minimum of basic training on the part of the laboratory technician.

It is suggested that monolayer culture pattern is useful in determining the dynamics of oesophageal cancer growth and may provide a prediction for all types of cancer.

Acknowledgements

The authors thank Sakiko Shimada for maintaining the cell culture, and Mr Tsuneharu Takeuchi (Chugai Pharmaceutical Co. Ltd.) for assistance in statistical analysis. The authors also thank Joanne Wilson for support in preparation of the manuscript and Dr Shunzou Maetani of the Research Center for Biomedical Engineering, Kyoto University, for advice in statistical analysis.

This work was supported in part by a grant-in-aid from the Japanese Ministry of Education, Science and Culture (grant 04670777) and the Japanese Foundation for Multidisciplinary Treatment of Cancer.

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British Journal of Surgery 1996, 83, 1152–1155

Plasminogen activators in oesophageal carcinoma

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The expression of components of the plasminogen activator system was investigated in patients with oesophageal carcinoma. Tumour and normal mucosa were obtained from resected oesophageal carcinomas and antigens were measured by enzyme-linked immunosorbent assay. Median levels of urokinase plasminogen activator (uPA) and the uPA receptor were higher in carcinoma than in matched normal mucosa (squamous cell carcinoma: uPA 4·05 *versus* 0·66 ng antigen per mg protein, uPA receptor 1·95 *versus* 0·50 ng/mg, $n = 10$, $P < 0{\cdot}05$; adenocarcinoma: uPA 2·16 *versus* 0·61 ng/mg, uPA receptor 2·01 *versus* 0·49 ng/mg, $n = 8$, $P < 0{\cdot}05$). Tissue plasminogen activator (tPA) level was lower than control values in squamous cell carcinoma but not in adenocarcinoma (1·97 *versus* 4·70 ng/mg, $P < 0{\cdot}05$). There was no difference in plasminogen activator inhibitor (PAI) 1 level between carcinoma and normal mucosa. The PAI-2 level was lower than that in normals in adenocarcinoma only (6·0 *versus* 64·77 ng/mg, $P < 0{\cdot}05$). These data support the hypothesis that membrane-bound uPA has a role in the breakdown of extracellular matrix in invasive oesophageal carcinoma.

Malignant cells must overcome a range of extracellular matrix barriers in order to invade host tissues and metastasize[1]. Degradation of extracellular matrix components by proteolytic enzymes is thought to be a key step in allowing the cell to migrate through the lysed matrix[2]. Several enzyme groups have been implicated in the lysis of extracellular matrix proteins, including serine proteinases, matrix metalloproteinases and cathepsins[3–5]. Plasmin, a serine proteinase, has a wide range of substrate activity, can activate latent forms of the other proteolytic enzymes[6] and may therefore have a central role in initiating an enzyme cascade which results in the degradation of all of the components of the extracellular matrix.

Plasmin is produced by the cleavage of the zymogen, plasminogen, through the activity of two serine proteinases, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA). uPA has a physiological role in invasive processes requiring tissue breakdown such as inflammatory cell migration, angiogenesis and trophoblast implantation[7–9], whereas tPA is essential for the intravascular lysis of fibrin clots[10]. uPA activity is considerably enhanced by binding to a specific cell-surface receptor (uPA receptor), allowing the cell a controlled, directional means of initiating pericellular matrix degradation[11]. The plasminogen activator system is regulated by the activity of specific plasminogen activator inhibitors (PAI-1, PAI-2) which bind covalently to the attached activator and cause internalization of the receptor–activator complex[12].

There is a growing body of evidence implicating the plasminogen activator system in the process of malignant cell invasion. Raised levels of uPA have been demonstrated in breast, colorectal, oesophageal, gastric and several other tumour types[13–20]. PAI-1 levels are raised in breast and colorectal carcinoma[13,15] but reduced in small cell carcinoma of the lung[18]. Similarly, PAI-2 shows variable expression, with increased levels reported in breast and colorectal carcinoma[21,22] but no difference in levels between malignant and benign tumours of the ovary[16]. Decreased PAI-2 expression is associated with poorer prognosis in patients with pancreatic carcinoma[23]. There are few reports of the expression of the uPA receptor in malignancy. Increased uPA receptor expression has been demonstrated in melanoma and breast, lung and colorectal carcinomas[24–28]. Expression of PAI-1, PAI-2 and uPA receptor has not previously been studied in oesophageal carcinoma.

Expression of uPA, uPA receptor, tPA, PAI-1 and PAI-2 was investigated in patients with invasive oesophageal carcinoma, comparing levels in tumour tissue with those in matched normal mucosa.

Patients and methods

Patients

Eighteen oesophagectomy specimens were studied (ten squamous cell carcinoma (SCC), eight adenocarcinoma) from ten men and eight women aged 51–80 years. Tumours were staged using the Union Internacional Contra la Cancrum tumour node metastasis (TNM) classification of 1992[29].

Tissue samples

Blocks of tumour and strips of macroscopically normal squamous mucosa were dissected from oesophagectomy specimens immediately after resection, frozen and stored at − 80°C for subsequent processing.

Sample preparation and antigen measurement

Samples were thawed and homogenized in 5 ml buffer (Tris 10 mmol/l, ethylenediamine tetra-acetic acid 1·5 mmol/l, glycerol 10 per cent, sodium azide 0·1 per cent). Whole cell preparations were made by centrifugation of homogenates at 800*g* for 15 min. Further ultracentrifugation at 100 000*g* for 45 min was performed to obtain cell membrane fractions for estimation of uPA receptor. Levels of uPA, tPA, PAI-1 and PAI-2 were measured in whole cell preparations and that of uPA receptor in cell membrane preparations using enzyme-linked immunosorbent assay kits (Bio-Stat Diagnostics, Stockport, UK, for uPA, tPA, PAI-1 and PAI-2; Alpha Laboratories, Eastleigh, UK, for uPA receptor). The lower limit of sensitivity for the assays was 0·1 ng/ml for uPA and uPA receptor, 1·5 ng/ml for tPA, 2 ng/ml for PAI-1 and 6 ng/ml for PAI-2. The total protein concentration (mg/ml) of each preparation was determined by Coomassie blue

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Presented in abstract form to the 81st meeting of the Surgical Research Society, London, 5–6 January 1995, and published in abstract form as *Br J Surg* 1995; 82: 702
Paper accepted 4 November 1995

assay. Antigen concentrations were then expressed as nanograms of antigen per milligram of protein.

Statistical analysis

Antigen concentrations in tumour samples were compared with those in normal mucosa from the same surgical specimen by the Wilcoxon signed rank test. Values below the sensitivity limit were given the same rank. Correlations between different antigen levels and between antigen levels and TNM stage were assessed by the Spearman rank correlation method. $P < 0{\cdot}05$ was considered significant.

Results

Of the ten SCCs, one was stage T_2N_1, three were T_3N_0 and six were T_3N_1. Of the eight adenocarcinomas, one was T_2N_1, two were T_3N_0 and five were T_3N_1.

The concentrations of uPA in tumours and normal mucosa are shown in *Fig. 1*. Median levels of uPA in both SCCs and adenocarcinomas were significantly higher in tumour samples than in matched normal mucosa (SCC 4·05 *versus* 0·66 ng/mg, $P < 0{\cdot}01$; adenocarcinoma 2·16 *versus* 0·61 ng/mg, $P < 0{\cdot}05$). There was a corresponding increase in levels of uPA receptor in tumours of both types (SCC 1·95 *versus* 0·50 ng/mg, $P < 0{\cdot}01$; adenocarcinoma 2·01 *versus* 0·49 ng/ml, $P < 0{\cdot}05$) (*Fig. 2*). Concentrations of tPA are shown in *Fig. 3*: tPA levels were lower in both tumour types compared with normal mucosa, although this difference was significant only in SCC (SCC 1·97 *versus* 4·70 ng/mg, $P < 0{\cdot}05$; adenocarcinoma 3·71 *versus* 5·44 ng/mg, *P* not significant). PAI-1 levels were below the limit of the assay in most samples and there was no significant difference between tumour and normal mucosa. PAI-2 levels (*Fig. 4*) were lower in tumour than in normal mucosa, with a significant

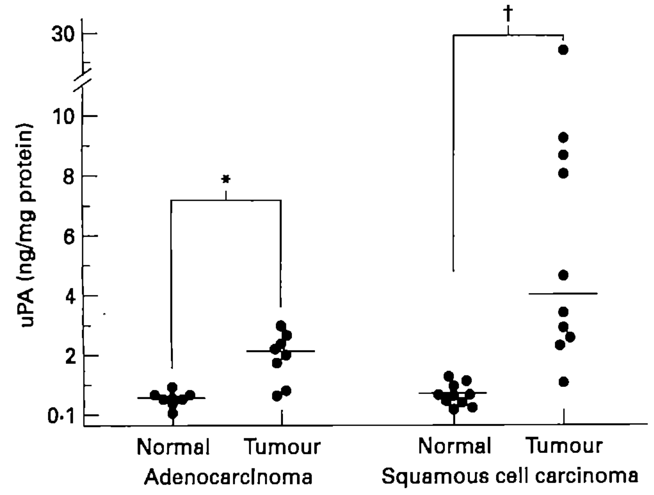

Fig. 1 Concentration of urokinase plasminogen activator (uPA) in normal and tumour samples from oesophageal adenocarcinomas and squamous cell carcinomas. Horizontal bars represent median values. $^*P < 0{\cdot}05$, $^\dagger P < 0{\cdot}01$ (Wilcoxon signed rank test)

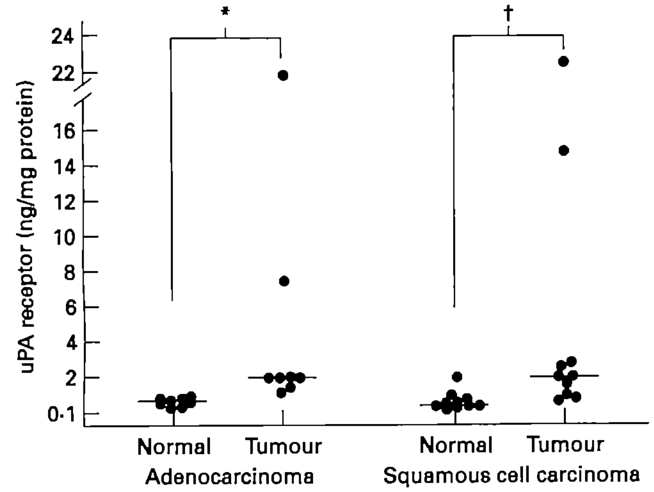

Fig. 2 Concentration of urokinase plasminogen activator (uPA) receptor in normal and tumour samples from oesophageal adenocarcinomas and squamous cell carcinomas. Horizontal bars represent median values. $^*P < 0{\cdot}05$, $^\dagger P < 0{\cdot}01$ (Wilcoxon signed rank test)

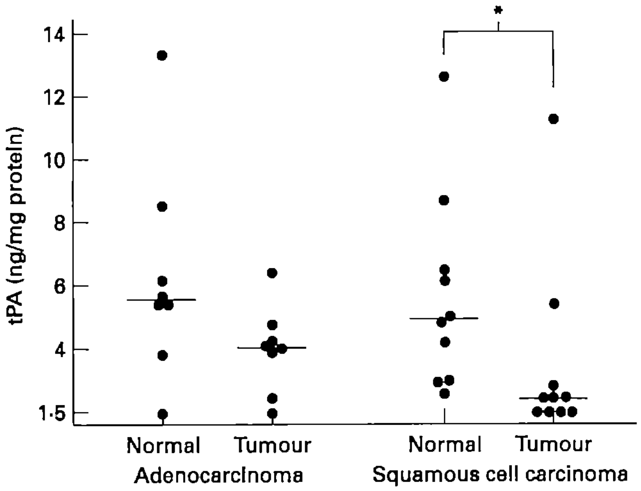

Fig. 3 Concentration of tissue plasminogen activator (tPA) in normal and tumour samples from oesophageal adenocarcinomas and squamous cell carcinomas. Horizontal bars represent median values. $^*P < 0{\cdot}05$ (Wilcoxon signed rank test)

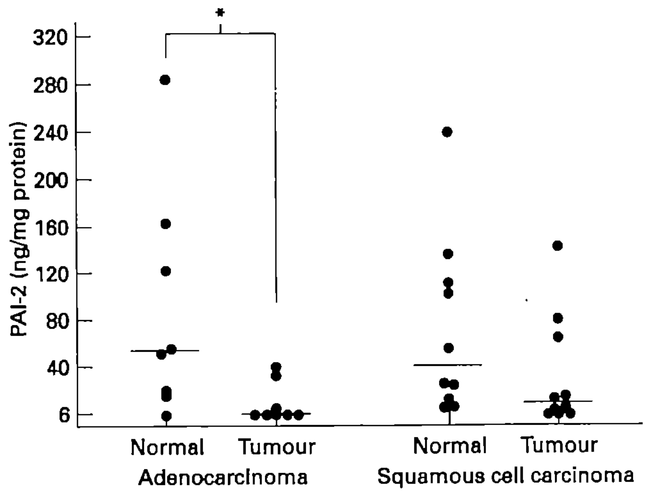

Fig. 4 Concentration of plasminogen activator inhibitor (PAI) 2 in normal and tumour samples from oesophageal adenocarcinomas and squamous cell carcinomas. Horizontal bars represent median values. $^*P < 0{\cdot}05$ (Wilcoxon signed rank test)

reduction in concentration in adenocarcinoma (SCC 10·68 *versus* 46·91 ng/mg, *P* not significant; adenocarcinoma 6·0 *versus* 64·77 ng/mg, $P < 0\cdot05$). No correlation was found between levels of different antigens for individual tumours, nor between antigen levels and TNM stage.

Discussion

uPA is one of a group of enzymes thought to be involved in extracellular matrix degradation during tumour cell invasion and metastasis[30]. Significantly higher levels of uPA were found in both adenocarcinoma and SCC than in control normal mucosa from the same resection specimen. uPA has a physiological role in many invasive processes[31] and increased levels in tumour samples may be a result of malignant cells utilizing uPA to initiate a proteolytic cascade culminating in the breakdown of components of the extracellular matrix. Cells of the monocyte–macrophage system produce uPA during migration[7], so raised levels in tumours may reflect an inflammatory infiltrate associated with the tumour. It has been shown in colorectal carcinoma that uPA is produced by stromal cells adjacent to invasive tumour nodules[32], although the cellular origin of uPA in oesophageal cancer remains to be determined.

A previous study[20] comparing uPA and tPA levels in oesophageal and gastric carcinomas with those in normal squamous and columnar epithelium showed increased uPA levels in both tumour types and decreased tPA levels in tumours of columnar epithelial origin. Levels of the plasminogen activator inhibitors and uPA receptor were not determined.

Recent evidence suggests that the activity of uPA is considerably enhanced by binding to a specific cell-surface receptor, allowing the cell to control proteolysis in the pericellular region[33]. Levels of the uPA receptor in the present study were significantly greater in both tumour types than in matched controls, although there was no correlation between uPA and uPA receptor levels for individual tumours. uPA receptor has been localized to tumour cells at the invasion front by *in situ* hybridization techniques in colorectal carcinoma[32]. Increased expression of uPA receptor may therefore be a characteristic of the malignant phenotype allowing the cell to bind uPA produced by the same cell, other tumour cells or stromal cells.

Levels of tPA were lower in tumour than in normal mucosa. Low levels in malignant compared with non-malignant tissue have been reported with various tumours[13,16,19]. Because the physiological role of tPA is primarily intravascular fibrinolysis rather than mediating invasive processes[34], levels may depend on tissue vascularity. If tPA acts mainly in the intravascular compartment, the low levels in oesophageal tumours may reflect decreased tumour vascularity compared with that in normal mucosa.

Plasminogen activation is regulated at several levels. uPA is secreted as an inactive precursor; binding to the uPA receptor enhances activity. The naturally occurring inhibitors, PAI-1 and PAI-2, bind covalently to the receptor–activator complex and block uPA activity[35]. Binding of the inhibitor results in internalization of the complex, allowing the cell to recycle the receptor to a different part of the cell membrane[12]. PAI-1 was not detectable in tumour or normal oesophageal tissue, although other reports have suggested slightly increased levels in colorectal and breast cancer and in melanoma[21,27,36]. Even in these tumours, however, the reported levels are very low. The present data suggest PAI-1 plays no role in blocking uPA activity in oesophageal carcinoma.

Previous studies have demonstrated variable levels of PAI-2 in tumours[16,19,22,36]. Reduced activity of this inhibitor, together with increased levels of uPA, in oesophageal carcinoma may result in an overall increase in plasminogen activation, culminating in more efficient degradation of the extracellular matrix. The cellular origin of PAI-2 has not yet been determined.

Changes in levels of components of the plasminogen activator system in oesophageal carcinoma compared with paired control mucosa support the hypothesis that oesophageal malignancy is associated with an increase in the level of cell membrane-bound uPA and a decrease in that of the inhibitor PAI-2. This may provide a mechanism whereby tumour cells can initiate pericellular proteolysis to allow invasion. The cellular origins of these components in oesophageal carcinoma require elucidation.

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British Journal of Surgery 1996, 83, 1156–1157

Randomized trial of blunt-tipped *versus* cutting needles to reduce glove puncture during mass closure of the abdomen

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Eighty-five consecutive patients were randomized to undergo mass closure of the abdomen with no. 1 polydioxanone mounted on either a blunt-tipped ($n = 46$) or cutting ($n = 39$) needle. Gloves were changed before closure and tested for perforation afterwards using standard air or water techniques. Fourteen pairs of gloves were punctured when using a cutting needle, and three pairs when a blunt-tipped needle was used. The majority of punctures were to the non-dominant glove. The surgeon was aware of the puncture in eight of the 14 instances involving a sharp needle and in one of the three involving a blunt-tipped needle. Blunt-tipped needles, while not eliminating the risk, significantly reduced the incidence of surgical glove puncture ($P < 0·001$, Fisher's exact test). The use of cutting needles for abdominal closure should be abandoned.

Surgical gloves provide protection from the hazards of contact with blood products but are often inadvertently punctured at operation. The reported incidence of glove perforation ranges from 14 to 73 per cent of procedures[1–4]. The surgeon may be aware of the puncture in as few as 15 per cent of cases[5]. The incidence of needlestick injury to surgeons is estimated at 5·6 per 100 procedures[5].

The risk of glove puncture during general surgery is highest during abdominal closure with a cutting needle, where perforation rates as high as 73·5 per cent have been reported[2]. Blunt-tipped needles are readily used for fascial closure[6,7] and would appear likely to reduce the incidence of both glove perforation and needlestick injury. This study aimed to test this hypothesis in a randomized trial of blunt *versus* cutting needles for mass closure of the abdomen.

Patients and methods

All patients who had elective colorectal surgery between October 1993 and October 1994 were recruited into the study. Surgery was undertaken by a single consultant or one of two registrars. Access to the abdomen was gained through a midline incision. In all cases abdominal closure was achieved by a standard mass closure technique[8] with no. 1 polydioxanone suture mounted on either the Ethiguard (Ethicon, Edinburgh, UK), taper point, blunt-tipped needle or a comparable cutting needle. Randomization to needle type was by random number generation. The surgeons were in the habit of 'guiding' the needle through the abdominal wall using a finger of the non-dominant hand, rather than adhering to a strict 'no-touch' technique.

Immediately before commencing abdominal closure the surgeon donned new gloves. If a glove puncture became evident to the surgeon thereafter, the gloves were immediately changed and tested. Otherwise, on completion of closure, each pair of gloves was examined for puncture using two methods. First, the glove was inflated with air and immersed in water, the escape of air bubbles being evidence of perforation[9]. Second, the glove was filled with water, its cuff folded to act as a seal, and the glove compressed, noting the source of any emergent jets of water indicative of puncture[10].

For the second half of the study additional testing was performed with a specifically designed electrical detection device similar to that described by other investigators[4,11,12]. This consisted of a battery-powered electronic circuit enclosed in a small case which was placed adjacent to the surgeon. After new gloves had been put on, and before commencing abdominal closure, this device was connected to an accessible part of the surgeon (usually the back of the neck) by an electrocardiogram electrode. The integrity of the gloves was then tested by placing the hands in a sterile metal bowl filled with sterile normal saline. The second lead was then connected to the rim of the bowl. Any breach in the glove resulted in a fall in the electrical resistance, and therefore completion of the circuit, which caused an alarm to sound. The gloves were tested in this way before and after closure.

Statistical comparison of the puncture rates observed after use of sharp and blunt needles was by Fisher's exact test for categorical data using a 2×2 table.

Results

A total of 85 patients were randomized to undergo mass closure of the abdomen with either blunt ($n = 46$) or cutting ($n = 39$) needles. Glove puncture rates, surgeon awareness, and involvement of non-dominant or dominant glove for both blunt- and sharp-profile needles are presented in *Table 1*.

Significantly fewer glove perforations were incurred using blunt needles than with cutting needles (three of 46 *versus* 14 of 39 respectively, $P < 0·001$). The surgeon was aware of the puncture in eight of the 14 instances involving a sharp needle and in one of the three involving a blunt-tipped needle; however, the small number of punctures in the latter group precluded statistical analysis. The majority of punctures were to the non-dominant glove regardless of the type of needle used (12 of 14 with a cutting needle, and two of three with a blunt needle). On no occasion did glove puncture lead to needlestick injury.

Presented to the Surgical Research Society in Manchester, UK, July 1995, and published in abstract form as *Br J Surg* 1995; 82: 1555

Paper accepted 7 October 1995

Table 1 Incidence of glove perforation, surgeon awareness and site of injury during mass closure of the abdomen using blunt and cutting needles

Needle	Pairs of of gloves punctured	Surgeon aware of puncture	Non-dominant glove punctured	Dominant glove punctured
Sharp ($n = 39$)	14	8	12	2
Blunt ($n = 46$)	3*	1	2	1

*$P < 0{\cdot}001$ (blunt *versus* sharp, Fisher's exact test)

The electronic detection device was used to examine the last 49 pairs of gloves but failed to reveal any punctures additional to those detected by air or water testing. A single pair of gloves was found on electrical testing to be perforated before use.

Discussion

This study confirms the high incidence of glove puncture after mass closure of the abdomen using a cutting needle. The present puncture rate was in fact lower than that reported by others[2,3,13], which may reflect an increase in care and attention fostered by the study, as well as the relative experience of the surgeons involved (a factor that may also account for the absence of needlestick injury). The surgeon's lack of awareness of glove puncture is once again a consistent and disturbing finding[5]. The use of coloured undergloves may help alleviate this problem[14].

As in previous studies[13,15] the majority of punctures were to the non-dominant glove, an observation readily accounted for by the practice of placing a finger of the non-dominant hand within the abdomen in order to guide the needle through the tissues. The adoption of a strict no-touch technique has been shown to result in a significant reduction in the rate of glove perforation[13], and this practice is recommended.

This study has demonstrated that the use of blunt needles significantly reduces the incidence of glove puncture incurred during mass closure of the abdomen. These findings were independent of the grade of surgeon (data not shown). The participating surgeons were unanimous in their assertion that this was achieved without any compromise in surgical technique. Penetration of the fascial and muscle layers of the abdomen with the blunt needle was achieved with little or no increase in effort, and abdominal closure was completed without delay.

One advantage of surgical gloves is to avoid exposure of the surgeon to potentially infected blood products. The risk of transmission of human immunodeficiency virus (HIV) by single inoculation injury is estimated at between 1:250 and 1:275, although most data refer to hollow needles[16–18]. The chance of transmission of hepatitis B and C is likely to be higher[19]. The risk of viral transmission after glove puncture in the absence of needlestick injury is less well defined. However, it is calculated that the risk of seroconversion for a typical surgeon with a 30-year career, working among a population with a 1 per cent prevalence of HIV, is approximately 1 per cent[20]. Any steps that reduce the incidence of glove perforation are beneficial.

This study has confirmed that blunt needles reduce glove perforation during mass closure of the abdomen. The continued use of sharp needles has no justification and places the surgeon at risk. Blunt-tipped needles should now be used routinely and should be extended, in combination with a no-touch technique, to embrace other areas of fascial closure.

Acknowledgements

J.E.H. is a University Research Fellow supported by AutoSuture UK.

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British Journal of Surgery 1996, 83, 1158–1159

Short note

Predeposit autologous blood transfusion in a tropical surgical practice

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The practice of transfusion medicine in the tropics is beset by problems of inventory and infection. It was decided to explore the feasibility of a predeposit autologous blood transfusion programme in a general surgical practice in a tropical environment.

Patients and methods

During 12 months all patients referred to a single surgeon (C.A.A.) who needed group typing and cross-matching of blood for elective surgery were studied.

Exclusion criteria were established as follows: patients aged over 60 years, haematocrit less than 35 per cent, uncontrolled hypertension, urgent surgery, jaundice, active infection, ischaemic heart disease, cardiac failure, myocardial infarction in the past 6 months, chronic respiratory disease, previous stroke, psychiatric illness, use of angiotensin converting enzyme inhibitors, sickle cell disease and human immunodeficiency virus (HIV) positivity.

After informed consent, eligible patients provided autologous donation based on the estimated transfusion requirement. Blood was donated within 30 days of surgery, at weekly intervals if more than 1 unit was required. The last donation was planned for 5 days before surgery. Oral ferrous sulphate supplement was given from the day of first donation. The decision whether to transfuse blood during operation was taken in consultation with the anaesthetist using standard criteria.

Unused predonated blood was assessed for suitability for homologous use and, if suitable, was then screened and transferred.

Results

Seventy patients were recruited, of whom 34 were ineligible. The reasons were: need for urgent surgery (12 patients) age over 60 years (six), presence of sepsis (six), jaundice (six) and anaemia (four).

Paper accepted 29 October 1995

Thirty-two patients (46 per cent) were eligible for predonation: six men and 26 women of mean age 37 years. The data from four patients were incomplete.

A median of 1 (range 1–3) units of blood was predonated (*Table 1*).

Two patients suffered transient dizziness and weakness after donation. In two patients the initially predeposited blood was transfused while a fresh unit was withdrawn on account of delay in surgery. Twelve predonated units (35 per cent) were not used: these were for patients having thyroidectomy, breast cancer surgery or cholecystectomy from whom only 1 unit of blood had been requested.

Five of these 12 units were transferred to the homologous blood pool, but the other seven were unsuitable because of use of antithyroid drugs (three patients), antihypertensives (two) or the presence of malignancy (four).

Three patients were unable to complete the outlined predeposit programme because of the distance they lived from the hospital.

The mean direct and indirect cost of each unit of autologous blood was $7.00 *versus* $25.00 for homologous blood.

Discussion

Voluntary donation as a source of homologous blood is not possible in many developing countries and patients often have to resort to procurement of blood from touts[1]. Concern about infections such as HIV and hepatitis has encouraged surgeons to explore alternative strategies[2], including acceptance of a haemoglobin level lower than 10 g/dl on discharge.

Another important strategy is the adoption of autologous blood transfusion practices[3]. Both direct and indirect costs were less in the present study, contrary to the situation in Western countries, where voluntary donors are plentiful[4].

Forty-nine per cent of these patients were unsuitable for predeposit autologous blood transfusion, 35 per cent due to the need for urgent surgery. For these patients preoperative isovolaemic haemodilution has now been incorporated into the authors' practice. Eighteen per cent

Table 1 Types of operation and blood use in eligible patients

Operation	No. of patients	Total estimated blood requirement (units)	No. of units predeposited	No. of transfused units	
				Autologous blood	Homologous blood
Thyroidectomy	16	20	8	2	0
Modified radical mastectomy	6	10	8	4	0
Breast reconstruction	3	6	4	4	1
Soft tissue sarcoma excision	3	22	8	8	10
Hemicolectomy	3	6	4	4	1
Cholecystectomy	1	2	2	0	0
Total	32	66	34	22	12

did not qualify on account of age, and an upper age limit is no longer specified, in accordance with practice elsewhere.

There was overdonation amongst those undergoing thyroidectomy, breast cancer surgery and cholecystectomy, and these patients are now considered for preoperative isovolaemic haemodilution.

Autologous blood transfusion currently provides 3 per cent of the total transfusion requirements in the USA, even though it has been estimated[4] that, when fully utilized, it could provide 10 per cent. Autologous blood transfusion is likely to have a greater role in the tropical environment.

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Corrigendum

L. Schlegel, C. Coudray-Lucas, F. Barbut, J. Le Boucher, P. Pernet, J. Giboudeau and L. Cynober. Long-lasting bacterial translocation and dissemination in a rat model after administration of a single dose of endotoxin. *British Journal of Surgery* 1996; 83: 861 (Abstract).

The value of nitrogen balance for ETX-treated rats which appears in the Table should read −96·4(60·5).

Erratum

Colonic decompression without on-table irrigation for obstructing left-sided colorectal tumours. D. C. N. K. Nyam, F. Seow-Choen, A. F. P. K. Leong and Y. H. Ho. *British Journal of Surgery* 1996: 83: 786–787.

The first sentence of the second paragraph in Results should read 'Median operating time was 115 (range 70–170) min for group 1 and 140 (range 75–240) min for group 2 ($P < 0{\cdot}05$, Mann–Whitney U test).

British Journal of Surgery 1996, 83, 1160–1163

Correspondence

Intravenous cholangiography reduces the need for endoscopic retrograde cholangiopancreatography before laparoscopic cholecystectomy

Sir

I read with interest the article by Mr Couse and co-workers (*Br J Surg* 1996; 83: 335) concerning the use of intravenous cholangiography (IVC) to reduce the need for endoscopic retrograde cholangiopancreatography (ERCP). Early in our experience[1] with laparoscopic cholecystectomy, lack of ERCP facilities prompted us to use IVC selectively to confirm absence of common bile duct (CBD) stones before laparoscopic cholecystectomy. There were only 13 patients, all women with a mean age of 32 (range 18–68) years. The indications for IVC were: presence of CBD dilatation on ultrasonography (five), abnormal preoperative liver function test (five), recent history of pancreatitis (one), acute cholecystitis with hyperamylasaemia (one), and no documented indication (one).

As shown in *Table 1*, IVC was negative in ten patients including the one with no documented indication (patient no. 6), and they underwent successful laparoscopic cholecystectomy. In one patient (no. 12) IVC was technically unsuccessful. The patient underwent laparoscopic cholecystectomy and ERCP and sphincterotomy was performed after operation for CBD stones. There was one false-negative result in another patient (no. 13) whose operative cholangiogram and postoperative ERCP revealed a CBD stone. In two patients (nos 10 and 11) IVC revealed slightly dilated CBD without filling defects (*Table 1*). Laparoscopic cholecystectomy was performed and they remained well throughout follow-up. There were no complications associated with IVC.

In our study, IVC was useful in excluding the presence of CBD stones in ten of 13 patients, eight of whom would have certainly needed ERCP according to our selection criteria. Our results also indicate that IVC can safely identify CBD stones before laparoscopic cholecystectomy in high-risk patients, especially in centres without ERCP facilities. However, IVC is inferior to ERCP as it is purely diagnostic and does not obviate the need for ERCP, which is also therapeutic if CBD stones are present. Its use as a screening test for ERCP, as suggested by Couse *et al.*, can be advocated bearing in mind the small risk of false-negative results and the greater workload it may add to a busy radiological department.

In our department, as easy access to ERCP facilities became available, our use of IVC to exclude CBD stones declined rapidly and has now become virtually obsolete.

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Table 1 Patient details

Patient no.	Age (years)	CBD on ultrasonography	LFTs	IVC
1	38	Dilated	Normal	Normal
2	68	Dilated	Normal	Normal
3	25	Cholecystitis, CBD not seen	Normal	Normal
4	18	Dilated	Normal	Normal
5*	40	Normal	Abnormal	Normal
6†	18	Normal	Normal	Normal
7	45	Normal	Abnormal	Normal
8	33	Normal	Abnormal	Normal
9	33	Normal	Hyper-amylasaemia	Normal
10	30	Dilated	Normal	Dilated CBD, no stone
11	19	Dilated + pancreatitis	Abnormal high amylase	Slightly dilated CBD, no stones
12‡	26	Normal	Abnormal	Unsuccessful
13‡	26	Normal	Abnormal	Normal. Filling defect on operative cholangiogram

*Converted to open operation due to difficult anatomy. †No documented indication for performing intravenous cholangiography (IVC). ‡Patient nos 12 and 13 underwent endoscopic retrograde cholangiopancreatography and sphincterotomy after laparoscopic cholecystectomy. CBD, common bile duct, LFTs, liver function tests

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Phlegmasia caerulea dolens and venous gangrene

Sir

In the discussion of the pathophysiology of arterial insufficiency in phlegmasia caerulea dolens (*Br J Surg* 1996; 83: 19–23), Mr Perkins and colleagues seem to favour the theory of arteriolar collapse resulting from an increase in tissue pressure and a decrease in intravascular pressure. This pathophysiological mechanism is similar to that widely accepted for the compartment syndrome. Several questions require answers.

1. The vessels that would collapse initially are the arterioles, with resultant injury to the nerves and muscles as they are most sensitive to ischaemia. Such muscle and nerve injury does not appear to occur, as demonstrated by the lack of systemic effect of myonecrosis and absence of residual muscle and nerve damage in the cases not progressing to venous gangrene.
2. The progression of gangrene from distal to proximal, and the frequently observed gangrene limited to the skin and subcutaneous tissue, is hard to explain.
3. Pulse deficit is noted in a large proportion of patients, implying an increase in tissue pressure within the compartments of the leg. The magnitude of such pressure increase has to be greater than the intravascular pressure of around 80 mmHg. Although pressure increases have been documented, they have been in the range 47–56 mmHg[1].

4. Furthermore, the true test of a proposed mechanism lies in the response to therapeutic interventions aimed at reversing the pathophysiological trend. Raising the leg high has been clearly documented to work but, theoretically, it should have a negative effect because it leads to a decrease in intravascular pressure that favours arteriolar collapse. Fasciotomy, on the other hand, should decompress the compartments with a reduction in the forces promoting arteriolar closure. This intervention is rarely recommended and, when used, has variable results. The argument, that fasciotomy wounds lead to infection and a wound that is difficult to close, is not borne out by the extensive experience gained in the compartment syndrome.
5. The main aim of using thrombolytic therapy is to produce lysis of the thrombus. Some authors[2] propose direct delivery of thrombolytics into the thrombus in the vein, with the belief that this obstructing thrombus leads to venous hypertension and the features of phlegmasia caerulea dolens. Other authors[3] propose intra-arterial and systemic therapy, reasoning that the underlying pathophysiology is the thrombosis in the venous capillaries. If the arterioles, as proposed, are occluded by tissue pressure, systemic and intra-arterial thrombolytics would not reach the site where they are most needed and would be of no benefit. However, recent reports have shown benefit with systemic, local venous and intra-arterial lytic therapy.

In the diagnosis of phlegmasia caerulea dolens the detection of cyanosis is emphasized. However, in dark-skinned people cyanosis is almost impossible to see, making the diagnosis difficult.

In summary, although no alternative pathophysiological mechanism is proposed, inconsistencies in the theory of arteriolar collapse are highlighted.

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A better bridge for loop stomas

Letter 1

Sir

Using a deep tension suture with its plastic sheath to support the loop colostomy is an improvement on the standard bridges (*Br J Surg* 1996; 83: 365). We would like to describe an alternative way of fixing the loop colostomy using no bridges at all. A nylon or polypropylene stitch is passed through the skin at a distance from the colostomy, then through the mesenteric defect, holding the needle back to front to avoid accidental injury to the bowel or mesentery, then through the skin inside out. Coming back through the skin the process is repeated in the opposite direction, thus tying a knot. This technique, while supporting the stoma, allows the loop of bowel when opened to be stitched to the surrounding skin leaving no gaps and allowing the colostomy bag to be fitted exactly around the stoma with the minimum of parastomal skin exposed. We have been using this method over the past 2 years; we have found it to be convenient to both patients and stoma nurses with no complications.

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Letter 2

Sir

I was interested in the article by Mr Cochrane *et al.* (*Br J Surg* 1996; 83: 365) regarding the use of a deep-tension suture as a bridge. I agree entirely with the comments made by the authors about the advantages of this technique over the conventionally available bridges. I have, for many years, used a similar technique but using a Jacques or a Foley catheter which is used to sling around the bowel to be brought out to manipulate it and pull it through for the colostomy/ileostomy and then use the same catheter as a bridge on either side of the stoma to the skin, having trimmed it to the exact size. I have found this a very useful technique and would consider it slightly more advantageous because of the different sizes of catheters that can be used, and also because of the softer exterior compared with the plastic of the tension sutures mentioned in the article.

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Molecular genetic basis of colorectal cancer susceptibility

Sir

We read with interest the Review by Messrs Cunningham and Dunlop (*Br J Surg* 1996; 83: 321–9) but take issue with two of the authors' conclusions. First, they state that non-gene carriers from families with familial adenomatous polyposis need never be enrolled in clinical screening programmes. However, these persons are still at risk of sporadic colorectal cancer, which may be about 6 per cent of the general population in Western industrialized countries[1]. Therefore, it would not seem to be justified to exclude these individuals from well tried clinical screening measures such as digital rectal examination. We agree with the authors that in hereditary non-polyposis colorectal cancer (HNPCC) clinical decision making is more difficult because this disease has incomplete penetrance and a well known tendency for affecting extracolonic organs. Without doubt, colonoscopic screening is indicated in all individuals at risk from families with HNPCC, where a mutation in HNPCC genes cannot be detected (about 30 per cent)[2]. The same may apply to families with HNPCC with mutations of uncertain significance (e.g. mis-sense mutations). However, given the theoretical possibility of coincident germline mutations in two or more HNPCC genes, the authors conclude that even in non-gene carriers from families with HNPCC, continued colonoscopic screening is to be recommended. Again we disagree: to our knowledge, simultaneous disease causing germline mutations in more than one of the four known HNPCC genes has not been reported so far. In HNPCC families, in which a definitive mutation can be identified to cosegregate with the disease, the risk of non-carriers harbouring a different but unknown mutation in other HNPCC genes equals that of individuals from the general population (one of 200, 0·5 per cent)[3]. As colonoscopic screening of the general population (with a 6 per cent risk of sporadic colorectal cancer) has not been recommended, we conclude that in HNPCC families with a definitive disease causing mutation, colonoscopic surveillance with its distress to patients and considerable health care expenditures[1] might not be recommended for non-gene carriers[2].

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1 Brown ML, Kessler LG. The use of gene tests to detect hereditary predisposition to cancer: economic considerations. *J Natl Canc Inst* 1995; 87: 1131–6.
2 Liu B, Parsons R, Papadopoulos N *et al.* Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. *Nature Med* 1996; 2: 169–74.
3 Papadopoulos N, Nicolaides NC, Ying-Fei W *et al.* Mutation of a *mutL* homolog in hereditary colon cancer. *Science* 1994; 263: 1625–9.

Authors' reply

Sir

We thank Dr Goessl *et al.* for their interest in our paper and are grateful for the opportunity to address their concerns. We agree with their comments on familial adenomatous polyposis (FAP), that non-gene carriers are still at the population risk of developing sporadic colorectal cancer. It would be appropriate for such relatives to be offered colorectal cancer screening on the same basis as the general population. Our recommendations refer specifically and exclusively to the avoidance of intensive screening, which is required for those at 50 per cent risk of FAP.

In an HNPCC family with a known mismatch repair (MMR) mutation, the issue of clinical surveillance in members shown not to carry the mutation is complex. We are of the opinion that at this early stage it is prudent to exercise caution in offering complete reassurance to those individuals who do not carry an MMR gene mutation. If an individual has been referred because of a strong family history of colorectal cancer, current clinical practice would include 2–3-yearly colonoscopic screening. The most important potential benefit of a genetic test is to indicate those who could avoid such intensive screening. However, where there has been an unusual aggregation of colorectal and other cancers in one family, it is simplistic to consider that an MMR gene mutation is the only determinant of cancer in that family. A number of environmental, genetic and epigenetic factors have come together to produce such families and, theoretically, this could even include segregation of more than one MMR gene mutation. We consider that two MMR gene mutations in the one family is an unlikely scenario, but nonetheless other factors make it possible that those family members who do not carry the mutation still have a higher risk. However, we do agree that it is reasonable to tailor clinical surveillance according to the results of genetic testing by reducing screening frequency for non-gene carriers.

There is no doubt that genetic testing for HNPCC has a central role in the clinical management of familial colorectal cancer. It will be of great interest to see how screening policies evolve with experience over the years to come.

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Local recurrence following total mesorectal excision for rectal cancer

Sir

It is with a weary sense of *déjà vu* that we read the paper by Dr Arbman and colleagues (*Br J Surg* 1996; 83: 375–9). They present an apparent improvement in local recurrence rates at 1 year after total mesorectal excision (TME) when compared with a selected historical control as evidence for TME as an oncological therapy in rectal cancer.

The history of oncological surgery is replete with examples of surgical techniques being advanced as superior in curing cancer when compared with inappropriate historical controls. Indeed in the same *BJS* issue Sagar *et al.*[1] illustrate the demise of Turnbull's claims made for the no-touch technique, based on historical controls, after proper examination of this technique in a randomized controlled study.

There can be no argument that meticulous surgery with clear resection margins should be of benefit in the management of rectal cancer. However, the specific role of TME as an oncological therapy remains unproven. Furthermore it is disingenuous to suggest that oncological therapies, such as preoperative radiotherapy, that have proven benefit in reducing local recurrence in prospective randomized studies, are somehow inferior to the unproven therapy of TME.

If the technique of laparoscopic colorectal cancer surgery can be examined within the context of a prospective randomized controlled study, then the oncological value of TME must be assessed with the same rigour. This is especially the case if the uncontrolled introduction of TME into rectal cancer surgery produces a 400 per cent increase in the number of patients requiring management and subsequent readmission for a covering loop stoma.

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Authors' reply

Sir

We thank Drs Scott, Carlson, and O'Flynn for taking interest in our recent article on the surgical treatment of rectal cancer. We could, however, wish that they had read it more carefully. Their remark that we used 'selected' historical controls is (fortunately) completely wrong. In fact, we started a prospective computerized registration of rectal cancer in 1984, and all data have been collected prospectively. Furthermore, Mr Scott and colleagues did not notice that the patient material is a population-based cohort from a defined area where every patient with a diagnosed rectal cancer was included. Comparing patients from two time periods can be criticized, as recognized in the article, but cohorts with no or at most minimal selection bias are less open to criticism in this respect. Information from cohorts certainly may reflect progress over time, which is the subject of this study.

Randomized controlled clinical trials should be used to evaluate new operations, but like many other colorectal surgeons we view total mesorectal excision (TME) as an improvement of the traditional operation and not a new operation. TME comprises strict dissection in defined anatomical planes, but the dissection is carried more distal than in the traditional operation. It results in more complete resection with clearer resection margins, especially the lateral margins, for tumours of the middle and lower rectum. This is a valid point as shown by the work of Quirke and co-workers[1]. Like many colorectal surgeons we find the TME operation to be technically more attractive and it seems consistently to provide local recurrence rates around 5 per cent. This is a great improvement also because it links surgical technique with recurrence. We are no longer in the dark about the means to reduce the historically high local recurrence rate.

We use preoperative radiotherapy (25 Gy in 5 days) routinely, but its benefit has not been established in the TME operated patients. Such studies are now initiated in Finland and Holland.

The protective stoma is again a separate issue. It may not be necessary in TME operations with a colonic pouch reconstruction, but it is our policy to protect the coloanal anastomosis. We would certainly welcome clinical trials that define the value of this practice.

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1. Adam IJ, Mohamdee MO, Martin IG *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994; 344: 707–11.

British Journal of Surgery 1996, 83, 1164–1165

Book reviews

Children's Medicine and Surgery

F. Cockburn, R. Carachi, K. N. Goel and D. G. Young. 267 × 197 mm. Pp. 539. Illustrated. 1996. London: Arnold. £39.50.

The management of the sick child very much involves a team approach, and the medical and surgical aspects of care often require input from both paediatricians and surgeons. A book covering children's medicine and surgery in a readable and well illustrated format is thus most welcome. It comprehensively covers paediatrics and paediatric surgery for the undergraduate, as well as providing essential reading for general practitioners. It will be of particular value for those in paediatric training, but should also be available to all general surgeons who have a paediatric component to their practice. New techniques as well as established methods are covered. The authors have successfully continued the Glasgow tradition of paediatric authorship, combining in this book a replacement for the late Professor James Holmes Hutchison's *Practical Paediatric Problems* and the late Wallace Dennison's *Surgery of Infancy and Childhood.* The whole subject is admirably encompassed in just 500 pages with clear line illustrations and excellent photographs, both in black and white, and colour. No references are provided nor are necessary in this text. More detail on specific topics can be obtained elsewhere if required. I recommend this fine paperback volume to all surgeons dealing with children.

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Principles of Operative Surgery. 2nd ed.

G. J. Poston. 215 × 138 mm. Pp. 246. Illustrated. 1996. Edinburgh: Churchill Livingstone. £15.

This book is unashamedly orientated towards the 'Surgery in General' examinations of the Royal Colleges and, as a *vade mecum* for the young surgeon facing these hurdles, it is first class. The contents are well informed, sensible and clearly laid out. It takes the form of a series of check lists for a comprehensive range of procedures and, in these days of super-specialization, it represents a real tour de force for a single author. My main criticism is the book's lack of emphasis on minimal access surgery. For the intended readership, I believe that some knowledge of the techniques and complications of laparoscopy is essential, but this was not covered to any extent. I was also a little surprised that gastrointestinal endoscopy was limited to an account of oesophagoscopy; a fuller description of gastroscopy and some mention of colonoscopy would have been welcome. These minor omissions aside, however, this little book achieves what it set out to do very well. If I were starting again, I would not be without a copy.

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Disorders of Thrombosis

R. Hull and G. F. Pineo (eds). 265 × 185 mm. Pp. 447. Illustrated. 1996. Philadelphia, Pennsylvania: W. B. Saunders. £96.

This is a very good book. A distinguished cast of mostly Canadian authors has been assembled to give a state-of-the-art review of the various aspects of arterial and venous thrombosis. The editors have been concerned to make the approach evidence based, and evidence for each comment is copiously referenced with the quoted trials rated on five levels, level 1 being large randomized trials with definite results, and level 5 being uncontrolled case series (according to Sackett). Even the references at the end of each chapter have been annotated to indicate what level of trial that particular publication refers to. This approach is extremely useful and should serve as a model for scholarly monographs everywhere.

The book is organized into two sections on arterial thrombosis and venous thromboembolism. Arterial thrombosis encompasses topics in coronary, cerebrovascular and peripheral vascular disease. The coronary section is exemplary, with exhaustive reviews of antiplatelet therapy, coronary thrombolysis and anticoagulation in ischaemic heart disease. Henry Barnett makes his customary strong statement in favour of carotid endarterectomy for the prevention of stroke. Gordon Lowe from Glasgow presents a balanced review of anticoagulant and thrombolytic therapy in acute stroke. The peripheral vascular section is possibly the weakest part of this book. There is only a very superficial discussion of thrombolytic therapy in acute arterial obstruction by Ouriel, which is less than would be expected by the main author of the TOPAS trial. The chapter on chronic arterial obstruction by Suggs and Veith is only a primer of lower-limb vascular surgery.

The venous section of the book is extremely strong. This is perhaps predictable given the number of objective trials in the area, but highlights include an overview of the prevention of venous thrombosis by Patrick Clagett and topical discussions of cost effectiveness in deep vein thrombosis prevention and diagnosis. Special problems, such as thrombophilia, pregnancy associated thrombosis, heparin associated thrombocytopaenia and the fate of isolated calf vein thrombosis, are extremely topical and coverage is useful even for experts in this field.

There is no question that this will become the major up-to-date reference for physicians and surgeons with an interest in circulatory disorders in general and thrombosis in particular. The vast number of controlled, semi-controlled and anecdotal trials in this area are beautifully reviewed and put into context. This serves as an excellent base for judging the work of future trials in this area and I have no doubt that this will form a well thumbed addition to my bookshelf in the future.

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Laparoscopic Colorectal Surgery

J. R. T. Monson and A. Darzi (eds). 283 × 222 mm. Pp. 269. Illustrated. 1995. Oxford: Isis Medical Media. £74.95.

This very handsome book is a timely addition to the currently available literature on laparoscopic colorectal surgery. The two editors, who are well known laparoscopists, have gathered an international group of equally eminent laparoscopic colorectal surgeons to co-write the chapters in their missionary zeal to excite all colorectal surgeons to take a more critical look at

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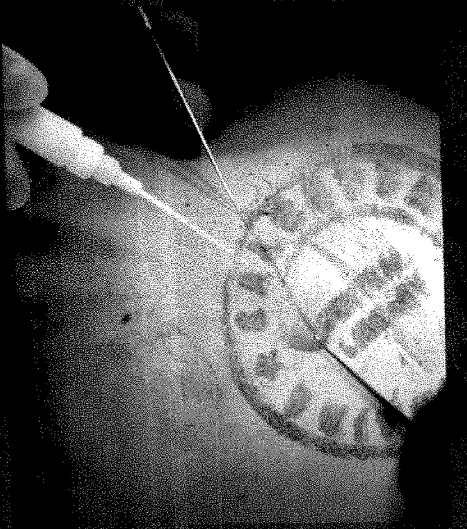

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